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Some Things We All Should Remember About Cancer

W. Walter Wasson, M.D.

Denver, Colorado

Certainly I can't present to this conference all of the things we should remember in our daily work with cancer. The things I have to offer have been an accumulation of a good many years and are more or less of a general survey.

In this paper, there is no attempt to present something new concerning cancer. It is a presentation of the various things which I, myself, find necessary to remember in the daily routine of the diagnosis and treatment of the cancer patient. Even after many years experience in treating cancer, I still find that on busy days I am apt to be too hurried in the examination of the patient or the diagnosis appears to be too evident. As a result, the treatment will be inadequate. In other words, I have made practically every mistake which anyone can make in the treatment of cancer. I think a little confession right at the beginning may be good for our patients.

What Is Cancer?

In the beginning, we may ask ourselves the question as to what is cancer. Certainly, there are various degrees of malignancy. The tumor may be malignant as to position in the body or it may be malignant as to its ability to produce metastases. Also tumors vary a great deal in their resistance to any form of treatment: surgery, radiation therapy or chemical therapy. We all recognize that there is a type of cancer which resists every present-day known method of treatment. Wherever found, a cancer cell is no longer subject to the growth controls of the body and has the ability to form metastases. In other words, the body has practically no resistance to the growth of cancer.

There are various theories as to the etiology of cancer. There is one theory that cancer is due to a mutation of a cell or cells as a result of inheritance, chemical changes within the body, or chemical irritation. Certainly there is plenty of proof that certain plants and animals can and do undergo mutation. It is a little difficult to understand why a large group of cells in a certain location in the body will all undergo mutation changes at the same time. There are those scientists who are beginning to think that the virus infections not only can produce cancer but can satisfy all the requirements of the origin and growth of the cancer tumor. If a virus is the cause of a certain type of cancer then our approach to the treatment of this type of cancer will be entirely different. Whatever may be the cause of cancer, its treatment must be considered as a major procedure. In other words, we should approach any case of cancer with the same care and precision that we would any major operation.

Accuracy in the Treatment of Cancer

Even the small cancerous lesion may have a catastrophic result. The physician in treating cancer must be 100 per cent accurate in order to obtain the desired result. Such a degree of accuracy is difficult to obtain and can only be had by industry and by meticulous attention to every detail in either the diagnosis or treatment. As just stated, I frequently find that I have overlooked some minor detail in either the diagnosis or treatment which later proves to be a determining factor in the ultimate outcome of the case. More and more, I am impressed by the necessity for meticulous accuracy in both the diagnosis and treatment of cancer.

Diagnosis of Cancer

In the diagnosis of cancer, as in any other disease, a good clinical history is the first step. Not only does the surgeon, internist, or radiologist wish to know whether or not the patient has a tumor but also the state of the patient's health. I think often we are apt to be so engrossed in the treatment of the tumor that we forget the general health. The patient must be considered as a chemical laboratory, and we are gradually learning more about the part chemistry

plays in the production of cancer and its treatment. The physician also wishes to know whether or not there has been recent growth of the tumor, and if there has been recent growth then that is a most important finding and means that the tumor is active. There are times when the clinical history is the deciding factor in the management of the case. For example, if a woman past the menopause has been free of vaginal discharge and then suddenly begins to develop a purulent or semipurulent discharge from the uterus, it is a strong indication of beginning malignancy of the uterine cavity. If a curettement of the uterine cavity is negative, or if a lipiodol examination of the uterine cavity is negative, and there is still an unexplained purulent or semipurulent discharge, proper consultation should be had, and a hysterectomy should be done. You will note that I speak of the proper consultation. It is much safer to do a hysterectomy at such a time rather than to wait for a more positive diagnosis. To await a positive diagnosis is to provoke disaster. Frequently there will be a small malignant ulcer involving the uterine cavity which cannot be detected by diagnostic methods.

The physical examination either of the cervix and uterus, or of a tumor of the breast, or of a tumor of the abdomen must be thorough but without trauma. Frequently the pathologist will report that the cancer cells are already in the lymphatic chains and ready to be transported to some other part of the body. Repeated examinations give invaluable information as to the progress of disease and as to the treatment which is to be instituted. Recurrent tumors after either surgery or radiation therapy require repeated examinations to determine whether or not there is still activity of the tumor cells. Such examinations are absolutely necessary for guidance in the subsequent treatments.

There have been various laboratory procedures devised for the demonstration of cancer. Papanicolaou's method for the diagnosis of cancer cells is one of the more recent and more refined. It evidently has its advantages in that only a few cells are necessary for a positive diagnosis, but it requires highly trained pathologists. At the present time there are only a few pathologists who feel qualified to make such diagnoses. A negative diagnosis by this method must be considered as any negative diagnosis by any other method while a positive diagnosis of cancer can be most valuable.

A Discussion of the Biopsy

A section of the tumor made by biopsy is still the most reliable single diagnostic finding. But even where there is cancer, it must be remembered that the section may be removed from a benign portion of the tumor, and it is impossible to section the entire tumor without removal of the entire tumor itself. In other words, it becomes extremely important from what portion of the tumor the section is taken. Again, the clinical history may be the deciding factor. I frequently see surgeons whose clinical judgment as to the probable malignancy of the tumor as determined from its appearance is almost of equal importance to that of a biopsy. Such a surgeon has the advantage of seeing the tumor in its entirety and *in situ*. I have seen such cases where the biopsy would be negative and yet the clinical appearance would be that of malignancy and would subsequently be proved to be such. Only recently I saw a woman with tumors in the breast, nodules in the axilla and above the clavicle, and with small skin nodules. Yet, a nodule removed from the axilla proved to be a fatty tumor, and a nodule removed from the skin revealed no cancer cells. Certainly, this patient is entitled to treatment for a malignancy of the breast.

Two years ago another patient presented a cervix that clinically was malignant, but upon which a biopsy made by the surgeon was negative. She was observed by the surgeon for two months and dismissed. One month ago, the same surgeon made a biopsy of the cervix of the same woman, and it was positive for cancer. What should have been the treatment of this patient two years ago: surgery, radiation therapy, or observation?

I come again to the thought that we should not always await a positive diagnosis of cancer by laboratory methods. To do so will often be disastrous and, in my opinion, is against the teaching of the early diagnosis and treatment of cancer. It is much better to remove the lesion which may become cancerous than to subsequently treat a definite cancer which carries a high mortality rate. No doubt many mistakes will be made, but the patient will not have assumed any great risk. In other words, I believe the risk in operating such cases at that time is less than the chance of error and the subsequent risk the patient would assume. It is needless to add that the treatment of the precancerous lesion by surgery, radiation therapy, or continuous observation should be carried out only under the control of proper consultation. It is not the responsibility of the individual physician. It does not mean that every woman should have a hysterectomy or her breast removed, or every man a prostatectomy. All tumors are not malignant, and all ulcers are not malignant, and an attempt should be made to obtain the correct diagnosis before any method of treatment is instituted.

Recognized Methods for Treatment of Cancer

There are three recognized methods of treatment of cancer: surgery, radiation therapy, and chemical therapy. Of these methods, surgery is usually, and perhaps rightly, given first consideration, the reason being that if a cancerous lesion can be removed sur-

gically without too much destruction of surrounding tissue then it is the method of choice. It is the method of choice because a cancerous lesion if entirely removed from the body has very little likelihood of recurrence. This statement is qualified as the factors which originally produced the cancer may not have been removed by the surgical operation. In cancer of the bladder, there is quite a tendency for recurrence after total surgical removal of the cancerous lesion and where it may be possible that the entire original tumor was removed. Whatever the predisposing cancer factors which produced the cancer in the bladder in the first place, they may not have been removed by the surgical operation.

Radiation therapy by x-ray, radium and the radioactive isotopes also has an important place in the treatment of cancer. Here the value of the treatment lies in the destruction of the cancer cells *in situ*. Whether or not radiation therapy should precede surgery, or follow surgery, or not be used at all, is often a controversial point and should be decided by consultation. In cancer of the breast, the place of radiation therapy has not been definitely established except in the third and fourth stage cases where the malignancy is already beyond the reach of the surgeon. Radiation therapy has proved its value in cancer of the breast, but if a nodule in the breast can be completely removed by surgery, then there again, surgery should be the method of choice. In the second stage cases with the involvement of the axillary nodes or the inflammatory involvement of the skin, it may be well to precede operation with radiation therapy. Whichever method is instituted, either surgery or radiation therapy, it must be adequate; and this means a careful examination and an accurate diagnosis.

Chemical therapy in the treatment of cancer is just coming into its own and is as yet rather poorly understood. However, there are enough good results from the use of testosterone in the female or of stilbesterol in the male to demonstrate the value of chemical therapy. I stated before that the patient must be considered as a chemical laboratory, and the general state of health plays a very important part in both the production of cancer and in the recovery derived from any form of treatment. Unfortunately, in many cases, the internist is not vitally interested in cancer, and the surgeon and the radiologist are many times deprived of the aid which the internist should be able to give.

The Follow-Up of the Cancer Patient

The *follow-up* of the patient after either surgery or radiation therapy is almost of equal importance to the original operation or treatment. The follow-up should be thorough, and accurate records should be kept rather than for the physician to depend upon his memory. For example, a woman has the left breast removed for cancer and is sent for radiation therapy following the operation. At the time of the examination preceding the radiation therapy, a nodule is found in the opposite breast. Fortunately, the surgeon's record states definitely that there was no nodule in the breast preceding the operation. Such a record is of vital importance to the patient. The time interval for the follow-up examinations should not, in my opinion, be every six months following operation or radiation therapy but every two weeks or one month immediately after surgery or radiation therapy. A six-months interval is only of value for statistics and of no value to the patient. The time interval should not be lengthened until several months have elapsed if the intent is to discover any recurrence and institute treatment of such a recurrence.

The Reactions from X-Ray Therapy

The reactions from radiation therapy are very poorly understood by most physicians, and I have been accused of producing everything from allergic shock to ingrown toenails. The x-ray is still mysterious. It is so mysterious that it receives the blame for almost anything that the patient may have after a course of radiation therapy. The radiologist should always be consulted before a statement is made to the patient by the attending physician. All the complications following known surgical or radiation treatment of cancer should not be considered as a result of the cancer, and yet this is so often the attitude of the medical profession. Recently, a patient with cancer of the cervix was treated by radiation therapy. Also, radium was placed in the cervix and uterus. The patient later developed dyspnea and also had an ulcer on the left shoulder with glands in the left neck. There were, also, inflamed masses in the gluteal regions. The pelvic examination was essentially negative, and an x-ray examination of the lungs was negative. The attending physician insisted that the patient had carcinomatosis. A week later an autopsy revealed a bronchoesophageal fistula which was not malignant. The ulcer over the left shoulder and the glands of the left neck were not malignant. The pelvis was negative except for some malignant areas remaining in the cervical canal. Cancer was not the cause of death. Neither should an attitude of hopelessness be assumed by the general physician upon finding that the patient has been treated for cancer. Careful study may reveal other causes of the illness which may lead to successful treatment and the recovery of the patient.

In general, it may be said that the failures in the treatment of cancer are due to getting the patient too late, or to inaccurate diagnosis, or to inadequate treatment.

Cancer of the Stomach

Walter L. Palmer, M.D.

Chicago, Illinois

The American Cancer Society estimates that at present there are approximately 193,000 deaths from cancer annually; in the next 50 years it is anticipated that the annual number of cancer deaths will rise to 324,000, an increase of more than 50 per cent. Cancer of the digestive tract causes more deaths than cancer of any other system. We do not know why cancer of the stomach or cancer of the other portions of the digestive tract is more common in the male than it is in the female.

Age plays a very important role as may be seen in the sharp increase and continued rise in deaths per decade after the age of 40. This illustrates again the dictum of Dr. H. G. Wells, former professor of pathology at the University of Chicago, to the effect that everyone would develop cancer if he lived long enough.

With regard to cancer of the stomach itself, we are all acquainted with the insidious nature of this disease. It does not begin as a catastrophic event even though it terminates as such.

To illustrate this point I will describe a patient and attempt to set the episode of carcinoma of the stomach against the background of his life. There were the ordinary colds and infectious diseases of childhood. For 15 years in middle life the patient suffered from chronic arthritis. At the age of 52 he developed bronchial pneumonia from which he recovered. Otherwise he was perfectly well.

In his 56th year, in March, he developed an ordinary attack of diarrhea and cramps such as any of us might have and as we all see in patients frequently. It passed after three or four days and was forgotten. In September of that year he had one transitory episode of vomiting, with no loss of weight, no abdominal pain, no anemia, no nausea—none of the classical manifestations of gastric cancer. In October, however, he had another transitory episode of vomiting followed by epigastric distress, not a severe pain, just dull discomfort different from anything he had had before. This, then, was a mild symptomatology, still no weight loss, still no anemia or anything of that sort; and yet, in November the x-ray of the stomach showed a carcinoma. The gastroscopic examination confirmed that diagnosis of a so-called Type III carcinoma, of the Borrmann classification. He was operated on in December, and a subtotal gastrectomy was done. That was at the age of 56. At the age of 59 he came into the hospital with a fever of unknown origin which disappeared and he was discharged feeling well. Now, at the age of 66, he is still alive and in excellent health. So here we have, among other things, a ten-year survival of a patient following resection of a carcinoma of the stomach. This tumor seems to have been a slow-growing, almost benign type of carcinoma.

A second patient illustrates exactly the opposite situation. In a man admitted to the hospital with minor symptoms of 18 months' duration, the x-ray examination showed a small niche on the lesser curvature (Figure 1). The symptoms on admission

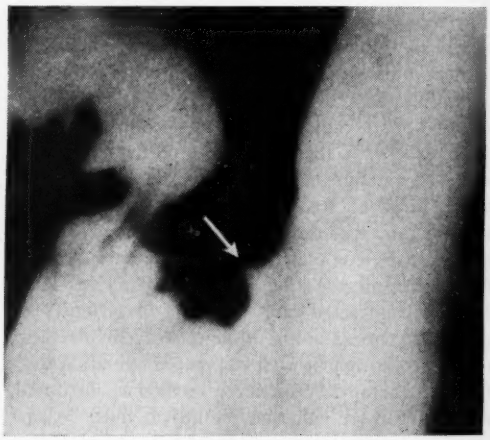

Figure 1. Small ulcerating neoplasm simulating a benign ulcer.

were primarily those of purpura haemorrhagica. His blood picture showed a severe anemia with the presence in the circulating blood of nucleated red cells, giving evidence of bone marrow metastases. The sternal biopsy confirmed this diagnosis. The patient died about three months later.

The interesting thing is that when the pathologist held the stomach in his hand and knew that the skeleton was riddled with metastases, he neverthe-

Figure 2. Low power. Cross section of the lesion. The architecture is that of benign ulcer but carcinoma is present in the mucosa on both borders and in the base.

less said that the lesion looked like a benign ulcer rather than a malignant one. It was an ulcerating carcinoma (Figure 2) which had metastasized rapidly, a so-called "rapidly metastasizing tumor of Jarko." Gastroscopically this ulcer did not look benign; it looked malignant. In the resected specimen, the architecture of the lesion was typically that of a benign ulcer. The entire muscularis was destroyed and replaced by scar tissue, but microscopically there were tumor cells visible throughout this scar tissue and on either edge in the mucosa. There was no reason at all to think that this was a so-called carcinomatous degeneration in a benign ulcer but rather that it had been a primary carcinoma of the stomach with peptic ulceration taking place in the tumor. The peptic ulceration produced a lesion which looked grossly like a benign ulcer and histopathologically had many of the characteristics of a benign ulcer, yet was from the beginning an ulcerative carcinoma.

There is also evidence that this lesion developed and spread in a very wild manner. It metastasized early. It seems to me that we can never expect to diagnose this particular type of gastric cancer in time to cure it with surgery. In between these two extremes of what might be called "chronic" and "acute" gastric cancer there is that great variation of tumors, some of which can be resected early enough for long survival and some of which cannot be. They might be called, shall we say, "subacute" cancer.

We are in the habit of trying to classify gastric cancers in terms of the old Borrmann classification. Borrmann Type I is a polypoid or medullated, non ulcerating tumor; it grows into the lumen. Type II is a localized ulcerated tumor. Types III and IV are ulcerative invasive neoplasms without a sharp edge or tendency toward localization. By and large, the Borrmann Type I and II cancers are relatively benign; they are much less malignant than the Borrmann III or IV, particularly the IV.

There is some sort of relationship, too, between gastric cancer, pernicious anemia and atrophic gastritis; it may be seen best, perhaps, in these Borrmann Type I tumors. The story of a particular case is illustrative. A physician developed pernicious anemia in 1926 with a red blood count of 1,500,000. Achlorhydria was present. Fortunately just at the right time Minot and Murphy announced the treatment of pernicious anemia with liver, so he ate liver and his blood count in three months rose from 1,500,000 to 4,500,000. The hemoglobin was normal. However, the roentgenologist had demonstrated a pedunculated tumor in the stomach; in November of 1926 the pedunculated tumor was removed.

It is of interest that this tumor when examined histopathologically was found to be an adenocarcinoma, judging from sections through the periphery of the polyp, but sections through the stalk showed no malignancy. The tumor was about the size of a small lemon. That was in 1926. In the period from 1926 to 1934 the patient faithfully took liver and later liver extract, and by so doing maintained a normal blood count. In 1934, although there were very few symptoms—a little tugging in the epigastrium —the x-ray examination was repeated and a tumor was demonstrated (Figure 3).

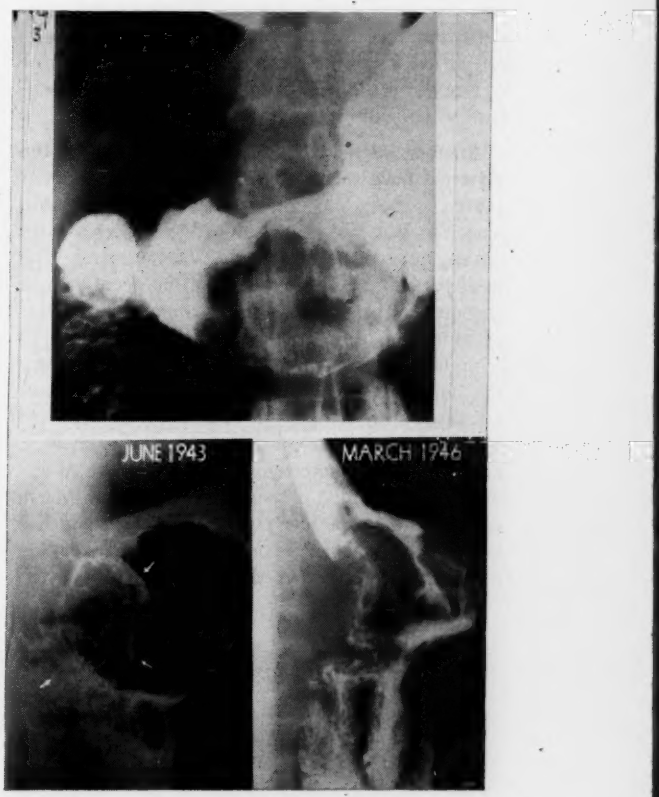

Figure 3. Polypoid carcinoma of the stomach resected in June, 1934, recurrent in June, 1943, causing esophageal obstruction in March, 1946. Patient failed to survive exploratory laparotomy.

A subtotal gastrectomy was done. A polypoid tumor was found and sections showed it to be a mucincus adenocarcinoma with extension through the wall of the stomach to the serosa, some involvement of the peritoneum, and involvement of the omentum overlying it. In spite of that fact, this man lived normally from 1934 to 1944 when a recurrent tumor was demonstrated in the gastric stump. He had a secondary anemia in 1944, caused by bleeding from the recurrent tumor, but no other symptoms. Even after the tumor was demonstrated in 1944 he continued to live. His blood count and hemoglobin returned to normal with the administration of iron.

Obstructive symptoms did not appear until 1946. He then died following an exploratory laparotomy. Death occurred then 12 years after resection of the cancer and two years after the demonstration of the recurrent tumor in the gastric stump. This story illustrates the very slow rate of growth of this particular type of tumor or at least of the tumor in this particular patient.

Now an interesting problem is why this tumor differed so in its growth from that of the patient who died from purpura haemorrhagica less than two years from the onset of symptoms. Is there a biological difference in the tumor? Or is there a factor of resistance on the part of the host? These are problems which will have to be resolved in the future.

Another instructive case is an exception to the picture I have presented in that a Type IV tumor proved to be a slow-growing lesion. This patient, who also was a doctor, had had a duodenal ulcer coming on after the first World War but manifesting itself particularly in the middle of the twenties with two massive hemorrhages. A gastroenterostomy was performed in 1927. Following this he got along well with no major difficulties. Sometime in the thirties he began to develop dyspepsia—a mild epigastric distress or "indigestion." Finally in 1941 he had an x-ray examination which was reported as showing a normal gastroenterostomy but nothing else of significance. The mild dyspepsia continued. In March of 1948 he lost a few pounds in weight and had three or four minor episodes of vomiting, so another x-ray examination was made.

The films taken in 1941, which we were fortunate in obtaining, showed the upper part of the stomach with normal rugal markings (Figure 4). Barium passed into the jejunum through the gastroenterostomy opening in a perfectly normal fashion but the antrum didn't fill. No barium at all went through the antrum into the duodenal bulb and into the second portion of the duodenum. It looked as though the patient had had a subtotal gastrectomy rather than a simple gastroenterostomy, but the surgical report was positively that of a simple posterior gastroenterostomy. By 1948, seven years later, the same condition was present in that there was no evidence of an antrum; barium passed from the stomach into the jejunum without difficulty, but a polypoid appearance was noted all along the lesser curvature. The rugal markings were completely lost, up to the fundus of the stomach which appeared rather normal. A mass was present in the left upper quadrant. Operation disclosed an infiltrating tumor involving all of the stomach. The rugal markings were lost because the whole stomach was infiltrated by a leather-bottle type of infiltration (Figure 5). The patient survived a complete gastrectomy very well, and the last I heard, some eight or nine months after operation, he was doing very nicely.

This then is the infiltrating type of tumor. It gives the poorest prognosis but in this patient it had obviously been growing for seven years; at least we do not know when it started.

If one surveys the problem of gastric cancer from the overall point of view rather than from isolated cases which I have been doing thus far, what is the picture? Two or three years ago we went over the

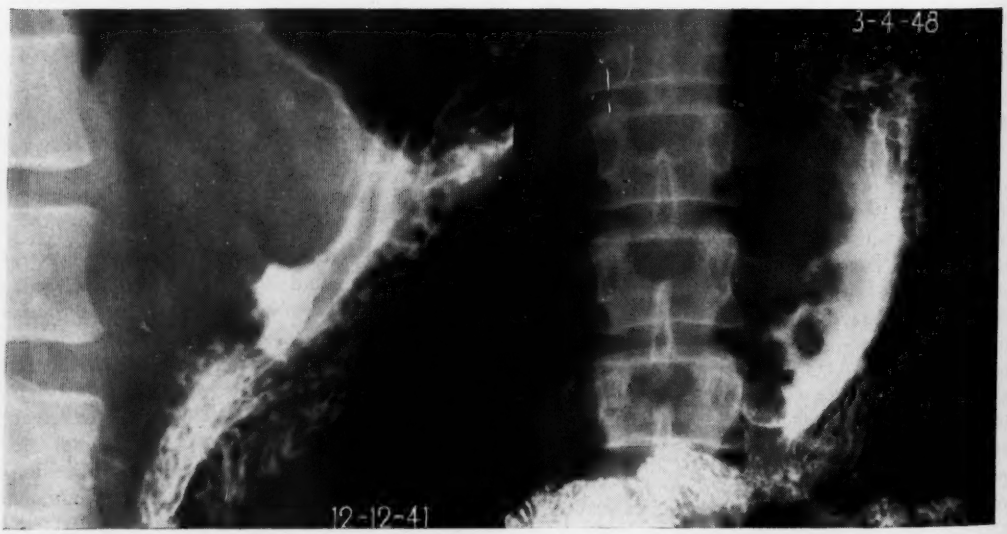

Figure 4. The appearance in the left view is that of a stomach after partial gastrectomy; the patient had had only a posterior gastroenterostomy; the antrum presumably was occluded by tumor. In the right view six years and four months later the same picture is seen and furthermore the rugal markings have been obliterated except in the fundic portion of the stomach.

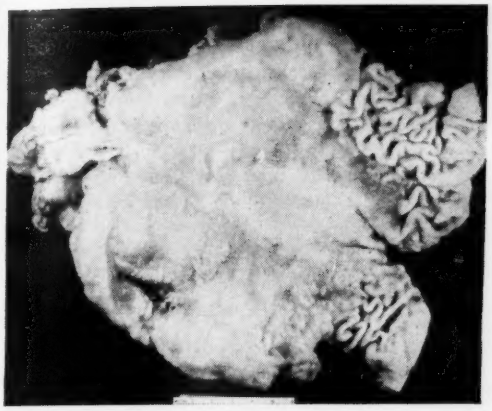

Figure 5. Total gastrectomy. The entire stomach is infiltrated with carcinoma except for the mucosa in a small portion of the fundus.

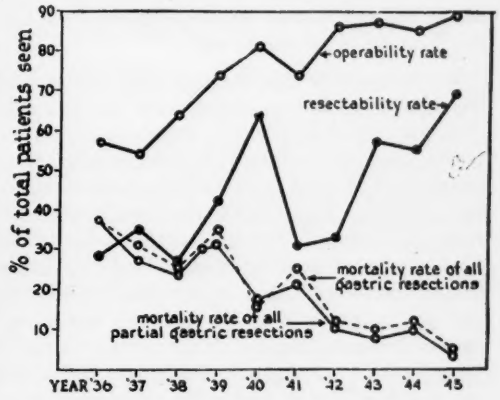

Figure 6. Operability, resectability and mortality in gastric cancer at the University of Minnesota (Wangensteen).

records of all the patients with gastric cancer admitted to our institution from 1927 to 1945, almost 20 years. We found 466 patients who had accepted the advice given. Of this group, 389 were subjected to operation. That means that nearly 80 patients were not advised to undergo operation, presumably because of contraindications.

My view at the present and through the past 20 years has been that all patients in whom a diagnosis of gastric cancer is made should be subjected to operation unless there are proved distant metastases. By that I would mean a carcinomatous peritonitis, Krukenberg's tumors of the ovaries, tumors in the liver, metastatic lymph nodes, or definite extension through the diaphragm into the chest. Even this view requires qualification. There have been rare reports of resection of a primary cancer of the stomach and of Krukenberg's tumors with long-term survival.

A word of warning may be given, too, with regard to the conclusion that metastases are present in the liver because a liver may be large; a liver may be firm and may appear nodular and yet the process be entirely independent of the carcinoma of the stomach. One can have benign cysts of the liver, fatty liver, or cirrhosis of the liver in association with gastric cancer.

In this group of 466, then, 389 or 83.5 per cent were subjected to operation. Resection was performed in 203; 150 survived operation. The fact that only one-third of the total group survived resection is in itself rather discouraging. If we compare the mortality and survival in two periods—from 1929 to 1940 and from 1941 to 1944—we find that the operative mortality dropped materially from 22.6 per cent to 16.3 per cent, and that the survival rate increased accordingly.

This point is further illustrated by statistics in a paper by Dr. Wangensteen of the University of Minnesota (Figure 6). In the period from 1936 to 1945 the operability rate increased from around 56 per cent to nearly 90 per cent; the resectability rate rose from a little under 30 per cent to nearly 70 per cent, and at the same time in spite of this rise in operability and rise in rate of resectability, the mortality from all gastric resections decreased from nearly 40 per cent to less than 10 per cent, illustrating again the tremendous advance made by the surgeons of the country in recent years.

RELATION OF TYPE OF TUMOR TO 5 YEAR SURVIVAL

Gross Classification of Gastric Carcinoma - BORRMANN	Incidence in all gastric Ca.	Incidence in 30 5 year survivors
TYPE I	2.9%	50.% (15 cases)
II	17.6%	43.3% (13 cases)
III	16.3%	6.66% (2 cases)
IV	63.2%	0

Figure 7. Classification of gastric cancer (Borrmann), incidence, and five-year survival.

Figure 7 emphasizes the statement with regard to the relationship of the type of tumor to the five-year survival. The pictures represent the Borrmann types: Type I the polypoid tumor without ulceration; Type II the sharply localized tumor, ulcerated; Type III the localized ulcerated tumor with some infiltra-

tion of the gastric wall; and Type IV with infiltration throughout the gastric wall.

We have studied gastric cancer with reference to this type of grading or classification and you will note that only three per cent, approximately, of all tumors come in the first type, 17.6 per cent in the second, 16.3 per cent in the third, and two-thirds of the tumors are Type IV. On the other hand, if we study our five-year survivors (approximately 30 patients), none of them fell within Type IV; 30 per cent of them were Type I; 56.8 per cent in Type II, and 6.6 per cent in Type III. It is only fair to emphasize, however, that one of the ten-year survivors was a Type III and that one patient described in this paper with a Type IV cancer had nevertheless probably had his tumor for more than ten years before it was removed.

Now with regard to the relationship between peptic ulcer and gastric cancer, I think that there is no evidence to indicate that benign ulcer ever undergoes neoplastic transformation, but the real problem, as Dr. McVicker said many years ago and as others have insisted, is the problem of differentiation between benign and malignant ulcers. That may be difficult. The surgeons tend to take the view that the only absolute sign is to put a section under the microscope and see whether the lesion is malignant or benign. There is a good deal to support this point of view, although I think that with careful clinical study one can arrive at an accuracy of diagnosis sufficient to justify treating many lesions as benign ulcers. But I have no quarrel, on the other hand, with the surgeon who prefers to remove them all, and certainly I would agree that any ulcerating gastric lesion ought to be considered malignant or probably malignant until proved otherwise either by most meticulous study or by removal. If all of the findings are in accord with the diagnosis of a benign ulcer, I am willing to so treat the patient temporarily and see how things go. But one must be very careful.

The presentation of an illustrative case may be helpful. A woman 41 years of age had had typical ulcer symptoms of 24 months' duration. There was no significant weight loss or anemia. An adequate free acidity was present. X-ray disclosed an ulcer of the lesser curvature with infiltration of the wall about the ulcer. Infiltration of this magnitude is almost pathognomonic of neoplasm, and the lesion looks like an ulcerating neoplasm. The gastroscopist also considered the ulcer to be malignant. The patient for entirely fortuitous reasons was treated medically for about two months. During this time the symptoms disappeared completely. It is important to remember that relief of symptoms on medical management occurs just as well in malignant ulcers as it does in benign ulcers. X-rays taken a month later disclosed a decrease in the size of the center, but that the infiltration or induction of the gastric wall persisted (Figure 8). In pictures taken still a month later, there was no evidence of ulcer but the

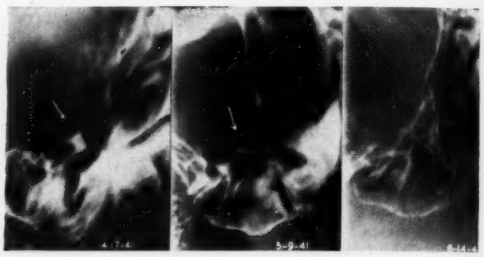

Figure 8. Ulcerating gastric cancer with disappearance of the crater on medical management. The deformity produced by the neoplasm persists.

abnormality in the wall persisted, suggesting the presence of a neoplasm with healing of the peptic ulceration. That is exactly what was found at operation by Dr. Brunschwig, in June of 1941, almost eight years ago. She is still alive and well.

The specimen contained a small ulcer not found by the last x-ray but healing was really complete. Neoplastic cells were present in the base of the ulcer and in the fibrous tissue over which the mucosa had regenerated. From this case and others there is clear evidence that healing of peptic ulceration in neoplasm can occur and that the defect may be covered with normal mucosa or with neoplastic mucosa. There are some types of gastric tumor which involve the gastric mucosa diffusely; they spread out through the mucosa. Ulceration can occur in these neoplastic mucosas and then heal.

I should like to conclude by making two points: (1) The symptoms of gastric cancer, as we all know, are in the beginning minimal—dyspepsia only. For that reason all patients with dyspepsia should be subjected to x-ray examination. The x-ray is our most valuable diagnostic method. Errors are made occasionally, but they are few. (2) I would emphasize again that all patients with gastric cancer, unless they have proved distant metastases, should be subjected to surgery with the hope and expectation that resection can be carried out. Resection should be carried out even though lymph node metastases are present because it has been well established that some of the long-time survivals are patients in whom tumor has been left behind in the lymph nodes or beyond the line of resection. Why these patients are able to survive for long periods of time isn't clear, but I presume it is related to the slow-growing biological nature of the tumor. The outlook for these patients is not entirely hopeless; they should have a resection.

Cancer of the Lung

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I am a pathologist and in the past pathologists used to be relegated to some dark and dingy corner of an institution. They were often difficult to find. They didn't seem quite respectable and they often carried with them a slight aura of formalin. I think that the pathologist of today has come out of the basement to some extent and is wandering around, talking to clinicians, and even seeing patients. I have been designated by some of my friends as a "Front Door Pathologist" because I always want every bit of clinical information I can get before I make a diagnosis and, therefore, if I speak at times of clinical matters to you instead of the gross and microscopic appearance of lung cancer, I hope you will bear with me.

I'm sure that you are all aware of the increasing importance of cancer of the lung, which has apparently greatly increased in numbers. This fact, correlated with the surgical advances in this disease, makes it of great importance. For instance, exploratory thoracotomy now carries with it a very low mortality rate and surgeons are now able to resect a lung with a very low operating mortality and with hope of cure (Graham, Jones).

There are many different roentgenologic, clinical, and pathological appearances of carcinoma of the lung. Carcinoma of the lung invariably begins in a bronchus which is centrally or peripherally located. If this bronchus is centrally located, the patient's symptoms begin as the bronchus is obstructed by the tumor. When the patient is first seen with a central malignant tumor of the bronchus, the signs and symptoms will be those of a respiratory infection, and many such cases have been diagnosed as tuberculosis, bronchiectasis, or unresolved pneumonia, and recently virus pneumonia has become a popular diagnosis. The shadow which is often demonstrated by x-ray is usually not the tumor, but result of the secondary effects of the tumor, with atelectasis, the abscess and even empyema. Such secondary inflammatory changes often clinically obscure the underlying carcinomas of the lung. In fact, *any peculiar or poorly explained pneumonic process which demonstrates an unusual clinical and roentgenologic behavior in the lungs of an older individual, particularly a male, should be suspected of being bronchiogenic carcinoma.*

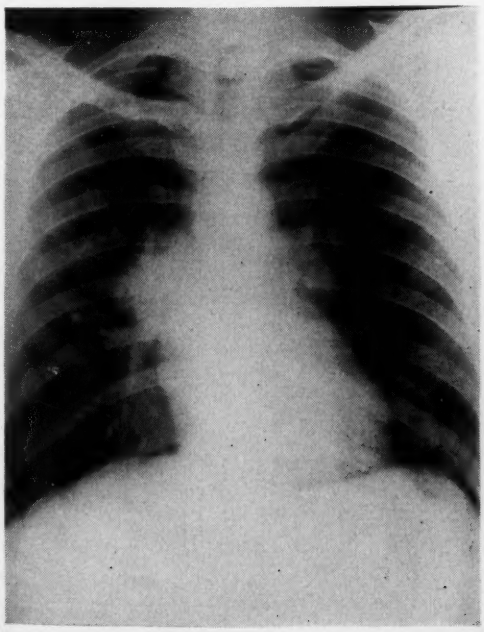

Figure 1—Radiograph of a centrally located bronchiogenic carcinoma with secondary shadows due to bronchial obstruction.

You also have adenocarcinomas of the bronchus that occur more frequently in women. If you eliminate this type of bronchiogenic carcinoma and speak only of squamous cell carcinomas, then a very high percentage of them, perhaps 90 per cent, will be in males.

In carcinoma of the lung, surgeons may speak of lobectomy for carcinoma of the lung. This is not a rational procedure except as a palliative procedure,

Figure 2—Gross photograph of surgically resected lung. Note large central fairly well delineated carcinoma arising from the large bronchus and growing out into the surrounding parenchyma.

not only because the lymphatic drainage is not of lobar distribution, but because of the local extent of the tumor along bronchi where it can grow beneath an intact overlying mucosa. We have had several cases in which tumor was restricted to the bronchi without evidence of lymph node involvement, but in which there was considerable extension along those bronchi. The bulk of the tumor may lie extraluminally but there may be considerable submucosal infiltration. The surgeon must resect such tumors far beyond what he can palpate grossly. The peripheral tumors have the same microscopic patterns as the central types but do not produce symptoms until an advanced stage, because they are arising from small peripheral bronchi.

These bronchiogenic tumors vary in their growth rate in the same fashion as the carcinomas of the stomach as discussed today by Dr. Palmer. It is certain that the growth rates of some carcinomas of the lung may be relatively slow (Goldman). We have seen a fair number of carcinomas of the lung with a relatively long history in which there have been changes in the bronchi suggesting that the tumor arose in an area of epidermoid carcinoma in situ.

Another slow growing but invasive neoplasm (the so-called bronchial adenoma) should be designated as a low grade carcinoma. This type of neoplasm occurs much more frequently in women, who often give a history of repeated episodes of bleeding. Graham has emphasized that such tumors should be treated surgically by pulmonary resection, not attempting to remove them through the bronchus. Most of these tumors have a large extra bronchial component and any attempt at bronchioscopic removal of necessity is incomplete. Such tumors rather infrequently metastasize distantly, but local invasion along the bronchus and metastases into the regional lymph nodes can occur (Anderson, Steiner). These tumors are entirely different from the usual carcinoma of the lung, and should be separated when one is talking about results of treatment. The tumors grow slowly, and usually arise in bronchi at least one cm. in diameter. This tumor is covered with intact mucosa, and if you bite off a bit of that mucosa through a bronchoscope it will quickly heal over. It will also bleed vigorously because such tumors are very heavily vascularized (Goldman). These tumors have an entirely different microscopic appearance than the usual carcinoma. They often have an organoid appearance and superficially resemble a carcinoid tumor. Individual cells have uniform small nuclei, and mitotic figures are rare. These neoplasms, however, make up only a relatively small proportion of all carcinomas of the lung (perhaps five per cent); but they do make up a fairly high proportion of the resectable and curable lung tumors (perhaps 25 per cent).

The peripheral bronchiogenic carcinomas are difficult to diagnose. If a tumor begins in a large

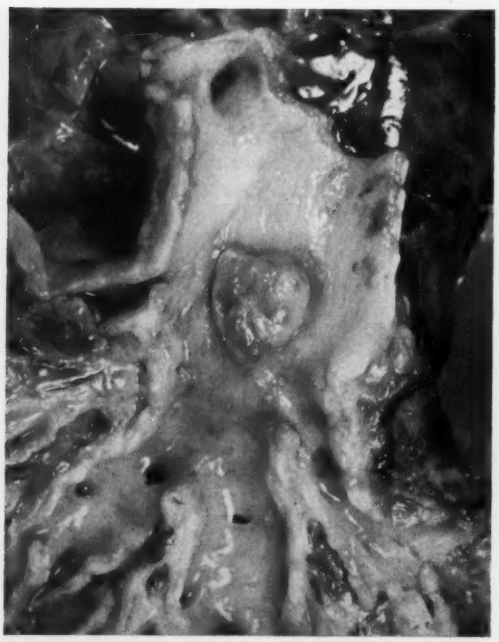

Figure 3—Pneumonectomy specimen demonstrating well delineated apparently intra-luminal so-called bronchial adenoma covered with intact epithelium.

Figure 4—This represents same specimen as Figure 3 cut to demonstrate the large extra-bronchial component with destruction of cartilage and invasion of lung parenchyma.

bronchus, the clinical signs are due to partial or complete obstruction of that bronchus. When a tumor appears in the periphery, the patient may have no symptoms. This is the type of case which is going to be picked up by these routine mass surveys which are being done primarily for tuberculosis. We are seeing more and more round shadows in the lung, and I can tell you that their diagnosis by looking at

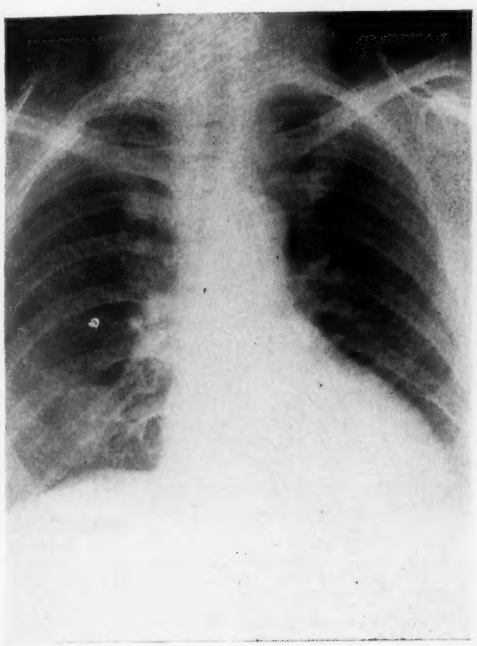

Figure 5—Round shadow right lower lung field. This was a benign tumor, a hemangioma.

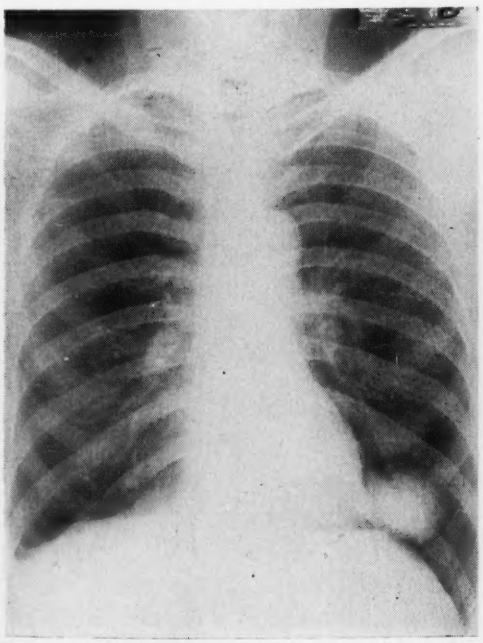

Figure 6—Round shadow, left lower lung field, containing small punctuate areas of calcification. This was a tuberculoma.

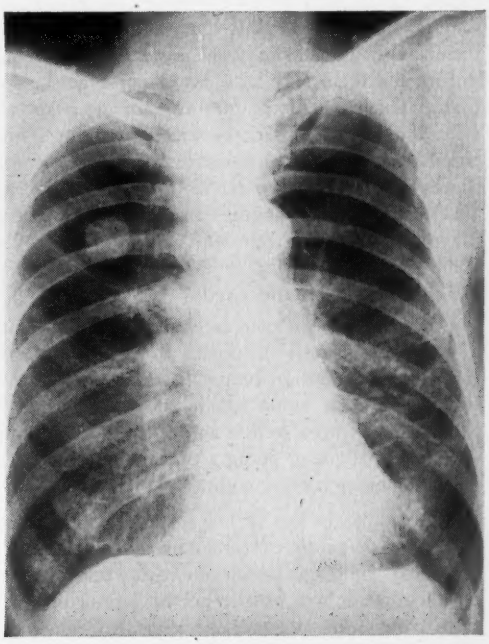

Figure 7—Round shadow, right upper lung field. Patient had no symptoms. This was a primary bronchiogenic carcinoma.

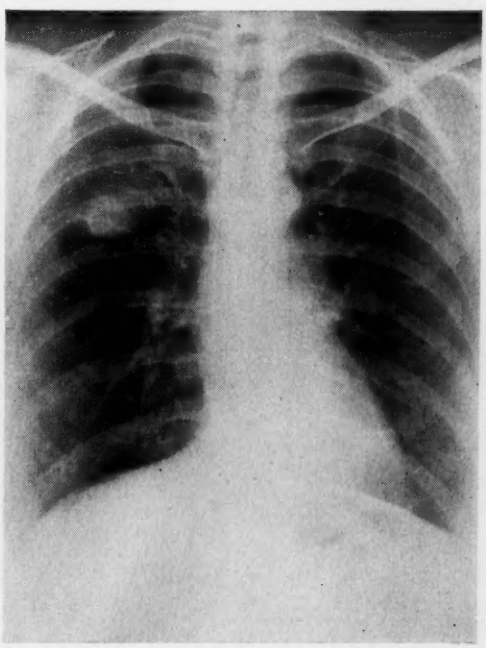

Figure 8—Round shadow, right upper lung field. Patient had partial obstruction of the esophagus due to a lye stricture. This round shadow was due to lipoid pneumonia.

the film is usually very difficult, if not impossible. Round shadows in the periphery may be caused by localized lipoid pneumonia, a tuberculoma, a metastatic neoplasm, a primary benign or malignant neoplasm. Often even with a complete clinical history, radiographs, laminography, sputa and bronchoscopy, the diagnosis remains in doubt. At times, with lipoid pneumonia there may be a history of ingestion of lipoid. The tuberculoma may contain punctate calcification. The metastatic neoplasm may give a history of removal of a primary tumor of the rectum, uterus or a soft tissue sarcoma several years before (Alexander). Such findings are suggestive but not diagnostic. Bronchoscopy will not be of value. In some instances, looking at the sputa or bronchial washings will make the diagnosis.

Our procedure on such cases, if we cannot make a positive diagnosis of cancer from the sputa or rarely from aspiration biopsy, is to explore such a lesion, resect the lesion locally and then look at it grossly, do a frozen section and proceed accordingly —if it is malignant, doing a pneumonectomy; if it is benign, being content with a local resection.

The pathologist can be helpful to the clinician in making a diagnosis of carcinoma of the lung. If you make the diagnosis by the history and physical examination, it will usually not be a positive diagnosis unless the patient has advanced inoperable disease. Bronchoscopic specimens are best blocked

Figure 10a—Tomogram of a peripherally placed shadow, left upper lung field, with central cavitation. This finding was picked up on routine chest survey.

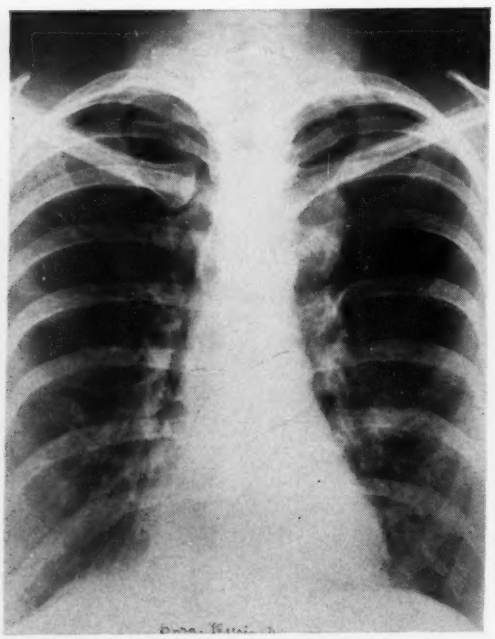

Figure 9—Round shadow, left lower lung field and rounded shadow close to the hilum left upper lung field. These two shadows proved to be due to metastatic leiomyosarcoma. Hysterectomy had been done four years previously for leiomyosarcoma.

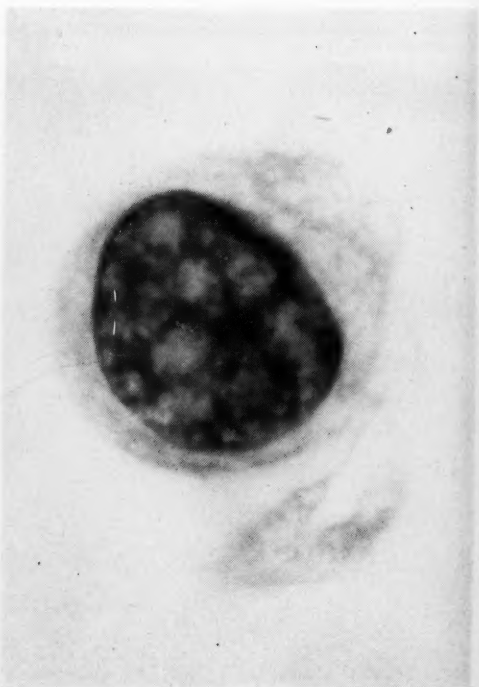

Figure 10b—Large cell found in the sputum with a very prominent nucleus and prominent nucleoli. This was interpreted as a carcinoma cell.

in their entirety and then cut at various levels through the block, and sometimes you will be able to make the diagnosis from one slide and not from any of the others. When you biopsy a tumor and it is an extremely undifferentiated tumor, then probably the chances are much greater that such a tumor has metastasized. However, if the tumor is biopsied and is quite well differentiated on its surface, it may very well be poorly differentiated in deeper areas. The percentage of positive bronchoscopic biopsies on any group of bronchiogenic carcinomas will decrease with increasing percentages of resectability. Exploratory thoracotomy with frozen section is often resorted to in order to make a definitive diagnosis. We do not use needle biopsy except in those instances where the patient has a tumor fairly near the pleura or has the so-called superior pulmonary sulcus tumor, in which an aspiration of the tumor can be made and sections can be done in the same way that you prepare ordinary sections (Meatheringham and Ackerman).

The cytologic diagnosis of carcinoma is a valuable laboratory procedure in the diagnosis of carcinoma of the lung. This method finds its best adjunctive use in those cases where the clinical signs and the symptoms suggest that a malignant neoplasm may be there, but in which a definitive biopsy cannot be obtained. It finds its least use as a screening procedure because it is extremely expensive, time consuming and requires considerable skill. In order for us to do sputa examinations, we trained a very good cytologist, Mrs. William Jackson, who had had a background in zoology. We also trained a pathologist, Dr. Ferrucio Bertoli, and both of those individuals have now worked together for over a year. We obtain three good specimens of sputa and/or bronchial washings, make several slides, then the cytologist, Mrs. Jackson, looks very carefully at all of those slides. She may spend all day long looking at four or five cases. If she finds areas which she believes are suspicious, she shows them to Dr. Bertoli. If he believes that the cells found suggest cancer, he shows them to me. I should emphasize that when we say that we find no evidence of carcinoma in the sputa that it certainly does not mean that carcinoma is not present. In any given group of lung carcinomas, the error in that regard probably is somewhere in the neighborhood of between 15 and 35 per cent, and that error will depend upon the type of case, the way the sputa is collected and the skill of the examiner. False positives should occur rarely. We have had only one instance, a case of lipoid pneumonia.

In lipoid pneumonia, unresolved pneumonia, bronchiectasis, chronic tuberculosis and other conditions in which squamous metaplasia may occur, bizarre cells may appear in the sputa which are extremely misleading. If you talk to cytologists with considerable experience in this area of investigation, they will all admit to you that they did have one case or two cases or even three cases in which they thought the sputa contained cancer cells but it did not. I think, therefore, that this method should receive its proper place in the diagnosis of cancer and should not be pushed on a higher plane than it deserves. We should look at the method carefully and judiciously and when it is added to the weight of evidence that has been submitted that the patient has carcinoma

Figure 10c—Gross specimen to demonstrate small carcinoma, left upper lobe. There were no lymph node metastases.

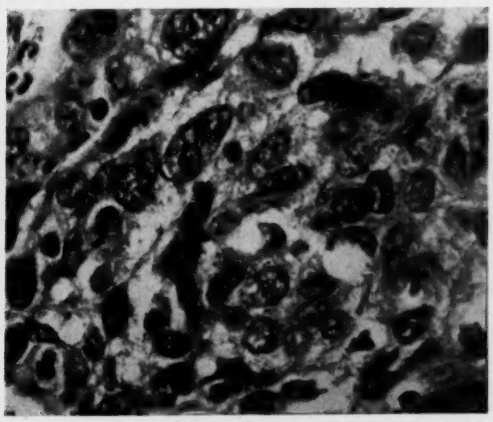

Figure 10d—Photomicrograph of the neoplasm. Note similarity of tumor cells to cell found in the sputum.

of the lung, we should merely drop it on the scale and have it take its proper weight. We shouldn't let it overbalance our judgment in the suggestion that a lung be removed.

The first patient who had his lung successfully resected by Graham is still alive, and this fact is eloquent evidence that bronchiogenic carcinoma is a curable disease. Careful attention to minimal signs of bronchial obstruction and increasing awareness that a peripheral round shadow in a chest roentgenogram may be a bronchiogenic carcinoma will lead to early thoracotomy, and therefore resection and cure in a fair percentage of instances.

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Tumors of the Ovary

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When given this subject of ovarian tumors, I became immensely interested because of the great pathological variation of tumors occurring in the ovary; on the other hand, I became hesitant because the thought immediately came to me that you can do so little about them. Fortunately they are tumors which do not occur too frequently in gynecology, but still we must discuss our weaknesses as well as our accomplishments.

In order to better understand the clinical approach to tumors of the ovary, it is necessary for us to have an understanding of the embryology of the ovary, and to recall that almost the entire reproductive and urinary system arises from the wolffian body and that this wolffian body lies in the posterior and dorsal position of the primitive peritoneal cavity. At a very early state in the development of the embryo there is an anlage of the so-called sex cells from which arise the sex glands. At one stage of the undifferentiation, it is impossible to tell whether this is going to be a male or a female gland. In the development there are some of the male vestiges that remain in the rete-ovarii which later may give rise to the masculinizing tumors which we refer to as the arrhenoblastomas. Also from these medullary columns of cells, which develop into the primordial follicles, we have vestiges of granulosa material that remain in the medula of the ovary and oftentimes in later life give rise to the so-called feminizing or granulosa cell tumors. Because we have these cellular arrests and we have connective tissue, epithelium and germinal epithelium and many other elements within the ovary, we have these unusual and bizarre tumors with which to contend.

Rather than go into the microscopic aspect of these tumors, I have chosen to consider them clinically, because I feel that whatever success we are going to obtain in the future is going to come from an early recognition of these tumors by a working classification which will be the basis for our selection of treatment. We have adopted in our clinic the classification of Novak. We agree with Novak that it is not the ideal; there are many fallacies, and if we want to base our classification on an embryologic or a microscopic study, this is not going to be accurate. On the other hand, if we base our classification entirely on the microscopic picture or the developmental study of the ovary, we are not going to have a successful clinical working division.

We divide tumors of the ovary, of course, into the cystic tumors and the solid tumors. Then we immediately divide these cystic and solid tumors into the benign and the malignant. The most common cystic tumors of the ovary are the benign follicle cysts and the luteum cysts which rarely attain a size larger than that of a lemon and require very little attention once they have been correctly diagnosed. Also we find frequently the germinal inclusion cysts and the endometrial cysts of the ovary which are, as a rule, in association with pelvic endometriosis. The neoplastic cysts of the ovary are the cystadenomas; the pseudomucinous, which are of the simple or the papillary variety, the serous cystadenomas, also of the simple or the papillary variety, and the dermoids, the benign form of the later teratomas. The solid tumors of the ovary include the papillomas, the fibroadenomas, the fibromas, the fibromyomas, the angiomas, lymphangiomas, chondromas, and osteomas. These are rare

tumors, but they are present because of the embryologic tissues which I mentioned a moment ago.

Of the malignant tumors of the ovary, the most common are the carcinomas. Variations of the primary solid carcinomas embody the adenocarcinomas, the medullary carcinomas, the carcinoma simplex, scirrhous carcinoma, alveolar carcinoma, and plexiform, or mesonephroma. The embryonic tumors include the granulosa cell tumors, the thecomas, the luteomas, the arrhenoblastomas, and the dysgerminomas, all arising in these tissues which are arrested, as I mentioned, in the male tubular elements of the rete-ovarii, while the granulosa cells are arrested mostly in the medullary portion. The cystic carcinomas are most frequently the pseudomucinous cystadenocarcinoma and the scirrhous cell papillary cystadenocarcinoma. We must never forget the metastatic tumors (the adenocarcinomas simple, the Krukenburg tumors, the epidermoid carcinomas, the hypernephromas), the teratomas, the sarcomas, and the melanomas.. Fortunately benign tumors of the ovary are the most frequent. They occur in our series in about 72.4 per cent of cases with malignant tumors in the remaining group. Comparing this with the literature we find, as a whole, 72.4 per cent to 79 per cent of the tumors of the ovary are benign and from 27.4 to 20.8 per cent of the cases are malignant.

Pemberton has accumulated a large number of ovarian tumors at the Free Hospital of Boston and has divided them according to their prevalence. He found that the pseudomucinous cystadenomas benign occurred in 21.4 per cent of this group of some 700 cases, while the pseudomucinous cystadenomas malignant occurred in 3.6 per cent; the serous cystadenoma benign occurred in 16.1 per cent while the serous cystadenoma malignant occurred in 17.3 per cent—very little difference between the benign cystadenomas and the malignant. The fibromas occurred in 10.3, sarcomas in 2.4 per cent, dermoids in 24.6 per cent, granulosa cell tumors in 2.9 per cent, Brenner's tumor in 0.9 per cent and the other rarer tumors in such small percentage that they demand very little consideration clinically.

When we are confronted with the clinical findings of a cystic swelling of the ovary, we must immediately classify that tumor, if possible, so that we can proceed with the selection of correct treatment. The follicle cysts, as I mentioned, rarely exceed the size of a lemon. They are not infrequently hemorrhagic because of hemorrhage occurring within the cyst cavity, and when this takes place there may be pain and discomfort. Otherwise they are usually symptomless. There being no characteristic symptoms, the only way we can discover these tumors is by routine examination. When found on routine examinations they should be watched. Tumors less than the size of a lemon that are symptomless, and which are probably follical or luteum cysts, certainly demand no surgical intervention. If, however, under close supervision, they are found to enlarge, to show growth activity, then most definitely do they demand surgical intervention.

The pseudomucinous and the serous cysts usually attract attention because of their size, and the size makes the fact evident to the patient that she has a tumor within the peritoneal cavity. These patients usually present themselves with the finding of an abdominal mass. Such rapidly growing tumors may cause the destruction of the uterus because of the destruction of the ovarian tissue, hemorrhage, irregular bleeding or a marked hypomenorrhea. If they have a severe destructive effect on the ovary, producing an associated hyperemia, the patient may have a menorrhagia. The patient complains of heaviness, pressure and enlargement of the abdomen. Its size and consistency immediately take it out of the realm of the simple cysts, which are thin walled, fluctuant, and easily manipulated, into the more doughy typical pseudomucinous or serous variety. These cysts may attain tremendous size. They have been reported as weighing as much as 378 pounds, although nowdays it is unusual to find them attaining a size larger than that of a fetal head because as soon as there is recognition by the patient she presents herself for care.

The complications which arise in these serous and pseudomucinous cysts, as they do in all cysts, are torsion of the pedicle, adhesions to the peritoneum, irritation causing local peritoneal response, with pain, leukocytosis and discomfort. Tumors of this size must of course be differentiated from pregnancy, tuberculous peritonitis, ascites, and myomata of the uterus. Frequently these tumors are so intact within the true pelvis that the uterus is pushed out

Figure 1. Serous cystadenoma.

of the pelvis and cannot be separately palpated. The tension of the pseudomucinous or serous cyst causes the feeling of density to be increased, and the mistaken diagnosis of myoma or uterine tumor may be made. It is always wise to differentiate by an exposure of the cervix and a probing in ascertaining the exact position of the uterus, the depth of the cavity, and, if necessary, by the injection of iodized oil and cystosalpingography.

The treatment of these tumors, of course, is surgical, because there is no way clinically of diagnosing the malignant from the benign. Surgical intervention should be immediate. At the time of removal of the tumor it should be examined both clinically and microscopically with a frozen section diagnosis. If frozen section diagnosis is not available, and there are papillary excresences on the inner surface of these cavities of the ovarian tumor, we most certainly must be radical. We cannot be conservative in a situation without more definite evidence, and it is better to err on the side of radicalism than on conservatism. When the tumors prove to be malignant complete surgery with removal of the uterus, the Fallopian tubes and the opposite ovary is indicated, because it is well known that malignancies of the ovary extend very rapidly into the uterus and to the opposite ovary. When I discuss the treatment of carcinomas of the ovary, further surgical procedures will be considered.

The solid tumors of the ovary are our most distressing group as far as end results are concerned. This is due to the fact that they are diagnosed late and that surgical procedures are often inadequate. We must remember always that carcinoma of the ovary is bilateral in 50.9 per cent, even though it may not be clinically evident. If we find a hard firm mass in the region of the ovary with some cystic degeneration occasionally within that hard mass (as occurs in certain of these tumors), there should be no hesitation to institute surgical procedures. A benign fibroma, or one of the other benign tumors, fibromyomas, myomas, etc., is far better removed, because of the chance of associated accident, torsion, interference with blood supply, etc., than to leave it behind and err again in having the malignant tumor misdiagnosed as a benign one. When a solid tumor of the ovary is diagnosed, the treatment is immediate surgery.

The prognosis in solid tumors of the ovary is poor. The five-year survival rate is approximately 15 per cent. Meigs in his group found 9.7 per cent survival in the solid tumors of the ovary, while in the cystic group he had a survival rate of 21.9 per cent.

The treatment of ovarian carcinoma is definitely surgical. If the tumor is fixed, is adherent to the peritoneum, or is adherent to the structures within the pelvis, preoperative irradiation often frees the tumor by causing the associated inflammatory reactions to subside, and when the tumor again becomes movable complete removal is indicated. We must realize, however, that when we are irradiating a tumor of the ovary of any size, or a tumor containing serous or mucinous material, we are deflecting the beam of irradiation and we are not obtaining, within the center portion of that tumor, the irradiation effect that we desire. Frequently you will see tumors that have been irradiated and regressed; then, within a very short period of time, they resume their activity and their growth. Therefore, if there is regression, and surgical intervention becomes feasible, that is the time when it should be instituted. We feel that even incomplete removal of an ovarian carcinoma is desirable because of the fact that obstruction is avoided and the remnants are more likely to be destroyed (or at least their growth temporarily arrested), by irradiation than if you are irradiating the entire tumor.

As to the extent of surgery, I believe one of the

Figure 2. Papillary serous cystadenocarcinoma.

Figure 3. Bilateral malignant granulosa cell carcinoma.

reasons that we have such poor recovery rates in carcinoma of the ovary is inadequate treatment by the first individual to see that tumor; procrastination after the tumor has been found, or as happens so frequently, unilateral oophorectomy because the true malignant character of the tumor is not recognized; and then a hesitancy to go back later in that same patient and do an adequate procedure, thus procrastination again. Irradiation is instituted with the hope that further surgical procedure will be avoided by its use. This can be seen if you break down the group of cases and compare those which have had proper primary treatment with those that have been inadequately treated and come for secondary treatment.

There should never be a surgical attempt on any tumor of the ovary unless there are facilities for immediate microscopic or pathologic diagnosis. Many of these solid tumors may be erroneously diagnosed as benign and without the true microscopic picture the proper treatment cannot be carried out. We find these very unusual solid, undifferentiated tumors in the young, 16 years of age with some either younger or older. We hesitate to do radical, thorough surgery, so a conservative operative procedure is carried out. If there is an immediate diagnosis and the surgery is complete and thorough, the survival rate naturally will be much higher. If the diagnosis of malignancy is made, even though the tumor is freely movable, not attached to the peritoneum or to other viscera, and no palpable lymph nodes are within the pelvis, one should still perform a complete removal of the uterus, the cervix and the opposite adnexa. I am of the opinion now that even a more thorough glandular dissection of the lymphatics within the true pelvis is indicated; and always a removal of the entire omentum, because of the high recurrence of these tumors within the omentum where it has, in all probability, only come in contact with the tumor, and the high percentage of local recurrent masses in patients who have had complete removal of the uterus, tubes, and ovaries. These things can possibly be avoided by a more radical attitude in the choice of our surgical procedures.

The question of post-operative irradiation is a debatable one. There are some of these tumors that are embryonic and of necessity radiosensitive. I am one who is of the opinion that if we do not accomplish anything with irradiation, we certainly do not in any way injure that individual, even though we may have inconvenienced her. Irradiation properly administered should cause a low percentage of bladder and bowel complications, and because of the fact that some of these tumors are radiosensitive, the patient should be given the benefit of thorough external irradiation post-operatively.

I do not feel that we can leave this question of ovarian tumors without at least mentioning a rare tumor, which is frequently misdiagnosed as ovarian in origin, and which again gives poor end results because of the fact that the true tumor is not recognized and the treatment is inadequate. I mean carcinoma of the Fallopian tubes. These are mostly rapidly growing highly malignant adenocarcinomas. Outside of the serosanguinous discharge, which is frequently present in the patient, there are no other symptoms in the early stages. The mass is found lateral to the uterus, or adherent to it, so the diagnosis is frequently that of a benign salpingitis, hydrosalpinx, hematosalpinx, etc., or an ovarian tumor. The diagnosis of this rare tumor is usually made by the pathologist, because the adnexal mass is removed. The tube is not open so the proliferation of the adenocarcinoma cannot be visualized and, therefore, the treatment is not thorough. Carcinomas of the Fallopian tube are rare. They occur in about 0.2 to 0.5 per cent of gynecological malignancies. They are reported by Livingston but 465 times in the literature, but the survival rate is extremely low. This can be corrected by recognizing

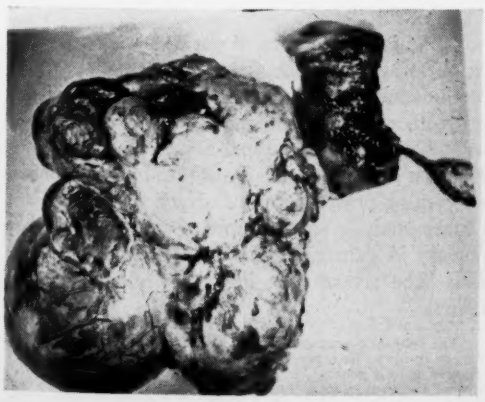


Figure 4. Dermoid and serous cyst ovary.

Figure 5. Fibroma (ovary cut in two).

that such tumors do exist and making an attempt at the time of surgery to arrive at the correct pathological diagnosis. There are too many specimens removed from the pelvis that are not sectioned or examined grossly at the time of the operative procedure.

Let me summarize these few remarks by saying that these carcinomas or malignant tumors of the ovary fortunately are rare; that good end results are rare—about 15 per cent surviving the five-year period; that I am of the opinion that the poor end results are due to inadequate diagnostic procedures, the patient presenting herself late in the disease, and the primary treatment frequently being inadequate.

There are homely axioms that can help us to remember certain things. I think the institution of the detection center—every doctor's office should be a detection center—is going to correct these poor end results. I think there are going to be earlier discoveries of tumors of the ovary and the pelvis. In order to remember that every woman presenting herself must have a pelvic examination, I like to say, "Greet all of your female patients with a pelvic handshake!" It carries a lot with it. It is surprising how high an incidence of pathology is discovered on routine pelvic examination. We should remember clinically that although the benign tumors of the ovary comprise about 73 per cent, the other 27 per cent are extremely dangerous. We must find them early, we must attack them completely, and the most successful treatment to date is radical, thorough surgery, possibly followed by external irradiation therapy.

Experimental Approach To Cancer Chemotherapy

Morris Belkin, Ph. D.

Bethesda, Maryland

I should like to present to you this afternoon some of the problems and findings of experimental cancer chemotherapy, to indicate the procedures which have been developed and the progress that has been made, and to do so from the standpoint of the research laboratory. In this way I hope to indicate the relationship and value of a cancer research laboratory to the cancer research clinic.

Historically, cancer chemotherapy has been in bad repute for many decades. It is a field which has been a favorite grazing ground for quacks, crack-pots and cranks of every stripe. Their fantastic claims could only be doomed to failure, with the result that for a long time the malodorous reputation of chemotherapy, though not deserved, frightened away careful, orthodox investigators from working with such problems. Also, the many and repeated failures of the early workers contrasting with the brilliant successes in the chemotherapy of many other diseases, led to a feeling of unjustified pessimism.

Recently, however, it has become quite respectable and even fashionable to engage in problems of chemotherapy of cancer, and the last two decades have seen a great increase in activity in this field.

One reason was the development of the proper laboratory tools for this type of work. The breeding of genetically inbred strains of mice, the discovery, the isolation in pure form, and the synthesis of chemical carcinogens, the increased availability of tumors, transplantable, induced, or spontaneous in origin, and the growing coordination of laboratory and clinical research, have all contributed to give this field a new impetus and direction. Work in cancer chemotherapy is currently going on in a number of institutions. This talk presents but one illustration of such investigation.

At the National Cancer Institute a program of cancer chemotherapy has been under way for the past five years, and I should like first to present and discuss the methods used, some of the difficulties encountered and some of the pertinent findings to date. I want also to say that this is a report of the activities of a large number of people trained in many different disciplines, who have been working together in the Chemotherapy Section at the Cancer Institute.*

The ultimate objective of our group is to develop chemical agents which either by themselves or in combination with surgery and radiation, will control tumor growth without causing severe and irreparable damage to normal tissue. Since there are countless chemicals available or possible of synthesis, a screening procedure was designed to pick out for further study a small number with demonstrable potency in damaging tumors in experimental animals. The several steps in the screening procedure follow:

*The following personnel in the Chemotherapy Section, National Cancer Institute, have been largely responsible for the investigation reported in this paper: Dr. J. L. Hartwell and Dr. D. L. Vivian, organic chemistry; Dr. J. Leiter and Mr. A. Perrault, toxicity and screening; Dr. R. C. MacCardle and Dr. V. Downing, cytology. Dr. M. J. Shear, Chief, initiated and directed this program.

After the appropriate vehicle for each substance to be tested has been selected, the maximum tolerated dose (M.T.D.) for a single subcutaneous injection is then determined. Values for LD_{50} (the dose necessary to kill 50 per cent of a group of mice) are also ascertained. These dose values are first secured for normal mice, and then repeated for tumor-bearing mice since it has been found that mice with tumors often will not tolerate as much administered compound as do normal mice.

The tumor employed is sarcoma 37 implanted in the muscle of the hind leg of strain CAF_1 mice. Using the preliminary toxicity data as a guide, a dose of the test substance is selected (near the M.T.D.) which is administered in the flank contralateral to the tumor in a single subcutaneous injection to 15 mice, bearing six-day implants. Fifteen mice bearing similar tumor implants serve as controls.

At eight, 24 and 48 hours, five treated mice plus five controls are sacrificed; observations are recorded on the gross appearance of the tumor and a slice of tissue fixed for subsequent histologic study.

Employing this procedure, which is essentially a simple method of selection, there have been screened so far over 1000 compounds. As expected, the great majority of these compounds showed no necrotizing action on our test tumor under our experimental conditions. Over 60 compounds, however, produced definite tumor damage following a single dose near the lethal.

These positive compounds fall into a number of major chemical categories, as follows:

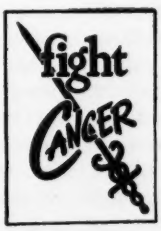
1. Colchicine and derivatives
2. Diphenylethylamines
3. Acridines
4. Quinones
5. Quaternary ammonium compounds
6. Trivalent organic arsenicals
7. Podophyllotoxin and related compounds

One of the consistent findings and difficulties is the toxicity of the doses which produce a tumor necrotizing effect. As with x-rays, the margin by which malignant cells are more sensitive than are the normal host cells to the chemicals studied thus far appears to be relatively small. For this reason, studying the possibilities of a variety of categories of chemical compounds has its advantage, among others, in that different compounds may strike at the tumor cell in different ways and hence possibly permit the use of a combination of agents to bring about a more powerful damaging action by exerting their effect through multiple pathways of cellular metabolism.

The results of our screening program have been to us encouraging. Five years ago we would not have expected that the screening of 1,000 chemicals would yield 60-odd compounds which had a definite effect, even at a near lethal dose, on a mouse sarcoma.

It should be pointed out that the 900 or more chemicals which we call negative are only so against our test tumor under the conditions of our screening operation with a single injection. Were we able to test each compound against a variety of tumors in a variety of animals and with repeated injections, the score might well be different. To do that, however, involves increasing the number of mice, staff, and space—problems in laboratory logistics which could not be accomplished.

From now on our program is to concentrate largely on the compounds found positive by our screening method. They will be given a thorough pharmacologic and toxicologic workup and, in addition, certain compounds are being tried against tumors other than Sarcoma 37 in order to obtain a more complete spectrum of their behavior. In the process most of them will probably be found unsuitable for human use, but we are encouraged to do further work and we hope that at least one or two will be of sufficiently high activity and sufficiently low toxicity so that the clinician would be justified in employing them for study in human patients with incurable cancer.



Carcinoma Of The Pancreas

Walter L. Palmer, M.D.

Chicago, Illinois

Carcinoma of the pancreas is a disease of considerable frequency, constituting two to three per cent of all cancer deaths. It is a disease for which there is no one specific pathognomonic sign, but on the other hand can be diagnosed without too much difficulty if one appreciates the clinical picture and if one bears it in mind. Someone has remarked that the frequency of the correct diagnosis of carcinoma of the pancreas is a good index of the astuteness of the clinician. The most important thing, I think, that the clinician needs to do is to keep the disease in mind. The question may be raised, of course, about why one should be so particular about trying to diagnose carcinoma of the pancreas if nothing can be done about it, and for that reason Dr. Brunschwig will spend part of the time assigned to me in discussing the surgical treatment.

The outstanding symptoms are pain and jaundice. Pain is even a more constant symptom than jaundice. It is usually epigastric, it tends to radiate through to the back, it may radiate more to the left than to the right, it may radiate around the costal margin. It may begin in the back and radiate through to the front; occasionally it is a generalized abdominal pain, occasionally it is referred to the lower abdomen rather than to the epigastrium. This pain, as the days and weeks go by, tends to be something of a neuralgic type of pain; it is persistent; it is not relieved by food nor by defecation. Sometimes it is relieved by changes in posture, but ordinarily not very much. It is a pain which may vary a good deal in severity from time to time but tends to be there—nagging or very severe. Sometimes it keeps the patient awake at night. In a few instances aspirin has afforded striking relief. Aspirin relieves a great many pains but when one finds an epigastric pain for which the patient takes aspirin, one should think very carefully about carcinoma of the pancreas.

Now with regard to the incidence of jaundice: in approximately two-thirds of our patients and two-thirds of the patients reported by other authors, jaundice occurred at some time. It is rather important to bear in mind that one-third of the patients with carcinoma of the pancreas will die without jaundice having been present. Sometimes jaundice is the initial symptom, but ordinarily we shouldn't wait until jaundice appears before we make the diagnosis.

Loss of weight is an important symptom. It was present in 72 of our 90 patients. It is ordinarily accompanied, of course, by loss of appetite, but not necessarily by profound anorexia, although that did occur in over half of our patients. Constipation was described in 29, but of course so many patients complain of constipation no matter what the disease that that isn't of much consequence. Nausea and vomiting occurred in 24.

I would like to emphasize diarrhea. There are a small number of patients who have carcinoma of the body of the pancreas who have a combination of pain, often lower abdominal pain, and diarrhea. That makes a rather puzzling syndrome—no jaundice, lower abdominal pain and diarrhea, and yet the diagnosis is carcinoma of the pancreas. It is a most difficult group to diagnose because one has to differentiate retroperitoneal tumors of other types such as lymphoblastomas and sarcomas, idiopathic steatorrhea, and similar disorders.

The traditional rule is that in addition to the two symptoms of pain and jaundice, one should have a palpable gall bladder. In about 50 per cent of the patients described in the literature the gall bladder was palpable; in our series it was palpable in only 39 per cent. So, again, if we wait for a palpable gall bladder to appear, we miss a great many patients. A palpable epigastric mass is present in only about one-third of the patients. So, again, we can hardly wait for an epigastric mass.

There are two other things that can be done in addition to these classical procedures that sometimes are quite helpful. One is to check the carbohydrate metabolism of the patient and the other is to x-ray. With regard to the carbohydrate metabolism, I've been surprised at the number of patients with carcinoma of the pancreas who do have some sugar in the urine. Marble has called attention to the rather high incidence of carcinoma of the pancreas in diabetics. It may be that some of these patients have diabetes of carcinomatous origin. About a year ago I learned a very bitter lesson of this sort. A patient came in with a loss of about 70 pounds in weight, glycosuria and a marked elevation of the blood sugar —the typical picture of diabetes mellitus. Without giving adequate consideration to the abdominal distress which seemed to constitute a minor complaint, the patient was transferred to the metabolic service. The diabetes was soon brought under control and the patient was discharged from the hospital. Within a few months he returned with jaundice, a palpable epigastric mass, and palpable gall bladder; to make a long story short—he did have a carcinoma of the pancreas from which he died.

Berk found that about 24 per cent of his cases had glycosuria; our own figure is 27 per cent. We were then led to check the glucose tolerance curve, finding that it was abnormal in a surprising percentage. Berk found it to be impaired in 78 per cent, another author in 100 per cent; our own figure was 80 per cent.

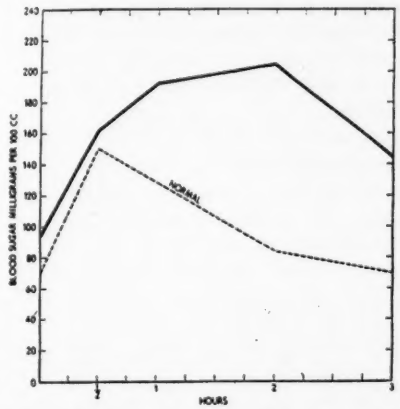


Fig. 1.—Composite dextrose tolerance curve of 21 patients

Figure 1 is a composite dextrose tolerance curve of 21 patients. The diabetic tendency of the curve is evident.

We were also surprised to see in reviewing our cases how many of them had had some type of an abnormality disclosed by x-ray.

The second portion of the duodenum may be displaced by tumor or it may be invaded. The infiltrated duodenum may undergo ulceration; massive hemorrhage may result. The process may simulate duodenal ulcer. In other instances obstruction may occur, usually in the second portion of the duodenum. The classical roentgenologic sign is enlargement of the duodenal loop due to displacement by tumor. In some instances the mass presents above the lesser curvature of the stomach, pushing the stomach down.

This discussion of the symptoms and the diagnosis of carcinoma of the pancreas may be summarized by saying that the important symptoms are pain, dull and steady as a rule, located in the abdomen, radiating to the back or not, sometimes radiating to the lower abdomen, accompanied usually by severe weight loss, loss of appetite, and occasionally by persistent diarrhea. The important signs, when present, are jaundice, palpable gall bladder, and an epigastric mass. The helpful laboratory findings are glycosuria, an elevated dextrose tolerance curve, and roentgenologic abnormalities of the stomach and duodenum.

May I conclude by again emphasizing the fact that probably the most important thing in the diagnosis of this condition is to keep the disease in mind, and that if one does keep it in mind, the clinical picture is so definite that there will be very little difficulty in diagnosis.

Now, with your permission, Mr. Chairman, I'm going to ask Dr. Brunschwig to continue with the discussion of the surgical therapy of carcinoma of the pancreas.

Surgical Therapy of Carcinoma of the Pancreas

Alexander Brunschwig, M.D.

New York, New York

There have been a good many questions raised about the techniques of surgery of the pancreas. There cannot be much said now which has not been said a number of times before in the literature and at previous meetings.

The principle of the resection of the head of the pancreas is well established. The statement has recently been made that cancers of the head of the pancreas have such a poor prognosis that one can seriously raise the question as to whether or not a short-circuiting operation might provide just as much longevity and comfort as the pancreatoduodenectomy which carries a high mortality. But the experience in attacking carcinoma of the head of the pancreas is not in vain because the same technique is applied to attacking carcinoma of the papilla of Vater or the ampullary region, or carcinoma of the lower centimeter or two of the common bile duct—all forms of cancer which, it would seem, afford a better survival following the radical operation.

I don't think that there is any question but that cancer of the papilla of Vater, if radically resected, offers a better prognosis than cancer of the head of the pancreas, and yet I do not think that we should subscribe to the principle that the radical operation should no longer be attempted in cancer of the head of the pancreas. Now there are perhaps 125 and there shortly will be over 200 cases of carcinoma of the head of the pancreas and ampullary regions treated by pancreatoduodenectomy recorded in the literature.

I think that the number of five-year survivals following radical pancreatoduodenectomy for cancer of the head of the pancreas or for ampullary cancer is indeed very few at the present time. Personally I know of three patients who have survived beyond the conventional five-year limit. Two of these are carcinomas of the papilla of Vater, and one of the head of the pancreas.

The question as to the best technique is hard to describe without a blackboard. The method that we now follow is essentially the technique that we described originally (1937), first an incision along the greater curvature of the duodenum to mobilize the head of the pancreas and thorough palpation of it between the thumb and the index finger to determine whether or not the superior mesenteric and the first portion of the portal vein are compromised. If they are not, then the stomach is transected low, near the pylorus, the superior pancreaticoduodenal artery identified, ligated and transected and the lower portion of the dilated common duct transected. Then the duodenojejunal junction is mobilized by transection of the ligament of Treitz. Everything is then freed except the neck of the pancreas and this is transected at the level of the superior mesenteric vein. In reconstituting the upper alimentary tract, a gastrojejunostomy is performed and a choledochojejunostomy performed further down the jejunum with an enteroenterostomy between the afferent and efferent loops to the choledochojejunostomy. Some have relatively recently advocated the re-implantation of the resected neck of the pancreas into the jejunal loop that goes up to the choledochojejunostomy.

There has been much discussion as those of you know who are particularly interested in this problem, concerning the methods of reconstituting the upper alimentary tract. The method I have followed does not include the implantation of the transected neck of the pancreas into the jejunum. Those who advocate its implantation do so because of the desire to return the pancreatic secretions to the jejunum and also to obviate the postoperative fistulae that develop when the neck of the pancreas is simply ligated and not implanted.

There is one additional point in favor of implantation of the transected pancreas into bowel and that is that the juice coming from the transected duct may contain carcinoma cells. If that's true, then certainly a fistula pouring juice into the upper abdomen and containing carcinoma cells would be a very undesirable thing, so that to obviate the fistula and to prevent the spilling of juice that might contain cancer cells, implanting the stump would be desirable.

Another factor of importance is that in a number of cases we have transected the neck of the pancreas, grossly very wide of the tumor, and yet a careful histologic study of the head of the pancreas and of the transected neck showed that at the level of transection there were lymphatics filled with carcinoma cells, not appreciable macroscopically. I think that the very poor results as far as long survivals are concerned for head of the pancreas might well be due in a number of cases to the fact that cancer of the head of the pancreas even though grossly small might resemble carcinoma of the breast in that it permeates rapidly the lymphatics of the whole organ. That raises the question which is being very seriously thought about now of doing a total pancreatectomy for any carcinoma that is truly in the head of the pancreas, just as one would not think of doing a partial mastectomy for a carcinoma in any one corner of the breast but take out the whole breast. I think very serious thought should be given to doing total pancreatectomies or subtotal pancreatectomies for any carcinoma which has arisen well within the parenchyma of the organ (not carcinomas of the ampullary region).

I do not think for a moment that we should give up with cancer of the head of the pancreas simply because our experience to date which is over a relatively few years has not yielded a greater salvage than it has and that we should reserve pancreatoduodenectomy only for the carcinomas of the papilla of Vater, the ampulla of Vater, or the lower portion of the common bile duct.

Cancer Of The Colon

Nathan A. Womack, M.D.

Iowa City, Iowa

Cancer of the colon always has been a relatively frequent cancer; yet, its recognition as a neoplasm has been relatively recent in our development of medical knowledge. Through the years it was considered a fibrotic stenosis and not associated with similar types of neoplasms in other parts of the body. During the past 75 years, its true nature has come to be understood. Its surgical removal, however, was replete with tragedy, and the operative mortality in large bowel surgery was so great that it was a form of extirpation practiced by only the most courageous surgeons.

Much of this picture has been changed during the past 25 years. Today we see a patient with a carcinoma of the large bowel with a great deal of hope. We can promise a very respectable operative mortality. We can even cure the cancer in a high percentage of instances. This change has come about in several ways, it seems to me. One of the most important is the fact that we now see a patient on the operating table who generally is in good physical condition with no obstruction and who has a clean bowel. Such a man can withstand surgery with a much lower chance of morbidity. Therefore, the various methods which we now have of preparing the patient for an operation have played a most important part in lowering operative morbidity and mortality. The decompression of the bowel, the sterilization of the bowel, the nutrition of the patient, the electrolyte balance, blood replacement, adequate and safe anesthesia all are things which have played an important part. Again, a significant advance has been made in our knowledge of the characteristics of early cancer of the large bowel and in technics of early recognition. It is particularly in relation to this latter phase that I want to limit most of my discussion this afternoon.

The technics of preparation of a patient and the operative removal of the segment of bowel that is diseased now are fairly well standardized. While we can anticipate still greater improvement as the years go by, our main progress must come from the early recognition of the disease.

A cancer of the large bowel is going to present itself symptomatically by virtue of the fact that it is an ulcerating mass. If it ulcerates, it is going to bleed. If it ulcerates, it also is going to become infected. Because it is cancer, it is going to invade. Our symptomatology then will be the result of ulceration, infection, hemorrhage, and invasion. The exact way in which these symptoms will present themselves to the patient will depend to a large part on that portion of the bowel in which the lesion exists. This situation has been oversimplified by the statement that tumors of the right side of the large bowel give anemia, diarrhea, weakness, and loss of weight; while tumors on the left side of the bowel produce obstruction. The statement frequently is true. Also, frequently it is not true.

Because the cecum and ascending colon have a much larger diameter than do the transverse, descending, and sigmoid portions of the colon, they can accommodate a much larger mass. Furthermore, the fecal stream on the right side of the large bowel is more or less of a liquid nature; and obstructive symptoms would not be expected to occur so early An appreciation of this purely anatomical situation, therefore, has resulted in the overemphasis of what seems to be an apparent fact.

It is important in the appreciation of symptoms of the large bowel that we take into consideration the motility of the bowel as well as its anatomical structure, for it is in alteration of the motility that many symptoms are produced.

Strangely enough, much of the motility of the large bowel still is poorly understood. Enough information is apparent, however, to be of considerable importance in understanding the symptoms produced by alteration of motility by malignant disease.

The cecum and ascending colon, for instance, play a most unique part in water absorption. This perhaps is not due to any particular difference in structure of the mucosa or the muscularis but rather to its type of motility. It will be recalled that as long as food remains in the stomach there is a tendency for the distal 15 or 20 cms. of the ileum to be involved in a stripping type of peristaltic movement in the form of a reflex action. This peristaltic movement forces the fecal stream into the cecum. The cecum itself has very little peristaltic activity. It does possess tone in its musculature, however, which plays an important part in its function. As the cecum fills as the result of the stripping action of the terminal ileum, it increases in diameter and also in length. The cecum will tend to descend for several centimeters into the pelvis. When distention reaches a certain point, tone begins to assert itself, and the cecum begins to contract slowly. This contraction produces a narrowing of the lumen, as well as an elevation of the cecum from the pelvis, and gradually forces the contents of the cecum into the

ascending colon. There a similar type of muscular action takes place. Normally, the fecal stream will stay in the cecum and ascending colon for from three to five hours before being pushed over into the transverse colon. When the fecal stream reaches the right part of the transverse colon, peristaltic activity begins and it is carried fairly rapidly across into the descending colon and sigmoid. It perhaps is due to the extent of time in which this fluid fecal stream remains in the cecum and ascending colon in intimate contact with a broad area of absorbing mucous membrane that much of the water is removed from the feces in this portion of the bowel. It can be easily understood that if an infected carcinoma exists in this part of the bowel, muscle tone will be increased markedly and the dilatation will not be as great. Then, there will be an acceleration of the emptying of the cecum and the ascending colon, and there will be less opportunity for water absorption. As a result, cancer of these two portions of the colon, as has been previously stated, may result in frequent soft stools. Relatively rarely does one see an annular constricting carcinoma of the cecum or ascending colon because of the enormous diameter of the viscus in this area. On the left side of the bowel where peristalsis is quite active and where an annular invasion is possible, interruption of the peristaltic wave is of frequent occurrence. This probably explains early obstructive symptoms in cancer in that portion of the bowel more so than actual occlusion of the lumen. Infiltration of the musculature plus spasm will tend to prevent a peristaltic wave from passing beyond the site of the lesion. Therefore, the obstruction is partly functional as well as partly mechanical. If we bear these mechanisms in mind, we can understand how carcinoma in the cecal area can produce symptoms resembling obstruction. If the tumor, for instance, invades that portion of the cecum adjacent to the ileocecal opening, it is easy to understand how the presenting symptoms will be those of obstruction, particularly of the type seen in the lower portion of the small bowel. Again, if the cecal carcinoma presents itself in the region of the orifice of the appendix, it is easy to see how the presenting symptom will be appendicular obstruction. Indeed, this is a much more frequent occurrence than the reports in clinical literature would lead one to anticipate. So frequently does carcinoma of the cecum present itself with the clinical picture of appendicular obstruction, and even with necrosis of the appendix, that one always must be on the lookout for this as the underlying cause of acute appendicitis in people beyond the age of 50. Again, if the carcinoma of the cecum is such that it has produced very little ulceration or secondary infection, there may be no diarrhea at all and the presenting picture may be one of a low-grade anemia with a palpable mass. Thus, carcinoma of the right colon may be most varied in its clinical appearance.

In a similar manner, carcinoma of the left side of the bowel may give a different clinical picture. For instance, in a patient who has a patent or incompetent ileocecal valve, obstructive symptoms often are rare and masked primarily by virtue of the fact that the patient receives abdominal cramps rather than nausea and vomiting. The competency of the ileocecal valve determines whether or not an obstruction of the large bowel will be a closed loop obstruction. Perhaps in one-third of the individuals, the ileocecal valve is competent and prevents a backflow of gas from the colon into the small bowel. In such an individual, therefore, obstruction of the sigmoid or descending colon will present rapid and profound distress. The nearer the obstruction is to the ileocecal valve, the more acute and the more extensive will be this distress. If such a process is allowed to exist for a considerable length of time, it is not an uncommon situation to encounter necrosis of the appendix from this obstruction or necrosis of the cecum.

An understanding of this mechanism gives us considerable insight into the therapeutic measures necessary as an emergency procedure in a patient with an obstructive lesion of the large bowel. If an x-ray film is taken of a patient in an upright position, a closed loop obstruction can be diagnosed by the absence of gas in the small intestine. Where such a situation exists, it is obvious that any effort to correct the obstruction other than by a direct opening into the large bowel will end in failure. We, therefore, have found it wise to do a right transverse colostomy immediately as an emergency procedure when these pateints are first seen. If the operation is delayed for 24 to 36 hours, it often is necessary to do the less desirable procedure of cecostomy. Where there is no closed loop obstruction and gas may be seen regurgitating into the small bowel, decompression as a general rule is possible with an indwelling catheter, either in the stomach or down into the small intestine.

Therefore, an understanding of the physiologic mechanisms involved in large bowel motility and an understanding of the effect on these functions when the gut wall is infiltrated with tumor tissue at a particular site or when there is infection, gives us an appreciation of the cause of the symptomatology in large bowel cancer. An understanding of the cause of the symptomatology makes it easier to recognize and interpret these symptoms when they occur.

So far we have concerned ourselves with the diag-

nosis of a well-manifest cancer. Our next problem is a consideration of those situations which exist, producing the so-called precancerous state. How can they be recognized?

Perhaps the most common of all precancerous lesions in the large bowel is a polypoid overgrowth of the mucosa. These polypoid growths, or adenomas, are composed of cells which tend to produce mucus. For the most part, they are columnar in shape and many of them form what apparently is perfectly normal mucus. In some adenomas, however, it is not unusual to encounter a type of cell containing cytoplasm with finely divided granules rather than mucus, while others resemble normal cells which have recently extruded mucus. Evidence of epithelial growth shows itself by hyperplasia and mitotic figures. Where this hyperplasia is active, ulceration is not infrequent, particularly if the growth is traumatized by hard stools. The microscopic picture of an adenoma of the large bowel, therefore, is one of abnormal growth in which the cells tend to considerable extent to resemble normal rectal mucosa. This is only a tendency. Some of them may be present for years, producing little or no trouble. However, others may appear rapidly, show considerably less evidence of growth control, and the clinical state of cancer frequently ensues early. It is difficult, therefore, to prognosticate the fate of a particular lesion. For clinical purposes, the main difference between the benign and the malignant adenoma is one of degree or extent. When an epithelial overgrowth invades, it is cancer. As a practical clinical expedient, one chooses the muscularis mucosa as the boundary line in determining invasion. Thus, where there is epithelial hyperplasia in an adenoma which has penetrated through the muscularis mucosa, we call it cancer. Where it has not invaded the muscularis mucosa, we call it adenoma. Let us now examine the evidence that we can obtain to establish the presence of such penetration clinically.

When the height of a tumor is greater than the diameter of its base, the tumor generally is benign. When the tumor is not attached to the muscularis mucosa, it can be displaced over the muscle layer with ease, and it, likewise, generally is benign. When a tumor begins to invade at the margins under the normal mucous membrane, the adenoma becomes not so clear cut; and the ulceration which so frequently develops remains permanent. The edema and inflammatory infiltration associated with such ulceration produce a lesion much more rigid and hard than the original adenoma. Thus, ulceration, induration and chronicity make their appearance. With these findings appear different symptoms. The bleeding becomes much less in amount but more constant. Inflammation with its sequelae may produce spasm of the bowel. The bowel wall becomes more rigid; and as the tumor becomes annular, symptoms of disturbed motility develop. A change in stool habits is often seen, and the picture becomes one of frank carcinoma.

Microscopically, these changes may be seen even more clear-cut. As one would imagine, when the growth becomes more sessile, microscopically there is evidence of lateral invasion. Also, one can clearly identify tumor cells going through and deep to the muscularis mucosa. With this entire picture, there often is an increase in growth rate. Where this occurs, there may be a lessening of differentiation. If so, enough evidence of this may be obtained by the morphologic characteristics of a particular group of cells. Often, however, this growth rate change is not so great as to be determined easily in such a way. It, therefore, may become necessary for the surgeon to excise the whole tumor in order to determine whether or not malignancy exists.

That the development of malignant change in these so-called adenomas may also be associated with the change in certain biologic characteristics in the cells is becoming more evident in experimental work going on in our Department of Surgery. During the transition of benignancy to malignancy we have been able to demonstrate in several instances of multiple polyps that there is an increasing inability of the cells to utilize oxygen. Respiration of the cell is interfered with markedly. The tissues apparently receive their oxidation by the process of glycolysis rather than the consumption of free oxygen. Effort to correlate these biochemical findings with the microscopic picture is beginning to show some fruit; and we hope that at a later date we shall be able to report on this phase of tumor growth in greater detail.

When we attempt to explain the origin of these focal areas of epithelial overgrowth in the mucosa of the large bowel, we encounter considerable difficulty. The vast majority of these lesions are single; and unless they ulcerate and produce serious bleeding, they usually are not detected until at a much later stage of their development. Where they exist in the rectum and can be observed proctoscopically, their growth has been noted at times to be slow and at other times to be quite rapid. Our effort to explain the origin of these single adenomas, however, still is most discouraging.

Certainly, some types of polyps or adenomas are hereditary. In stable communities where single families have lived for several generations and, therefore, where they can be followed, definite hereditary evidence exists particularly in the multiple type of

disease. At the University Hospitals in Iowa now we have a number of such families we have been able to follow for several generations. The inheritance of this factor which tends to produce adenomas seems to follow Mendelian principles, and the factor seems to be a Mendelian dominant one. We have several families in which neither the parents nor any of the grandparents have had a history of large bowel disability, while all of the siblings of the third generation have had multiple polyposis. This suggests that there may develop a genic mutation of a dominant nature.

Another very impressing observation in these patients that we have studied is the age at which the multiple adenomas have changed into cancer. We have two such families in which no member has lived longer than the age of 30 without having developed a cancer of the large bowel. We have another family in which the cancer has not occurred until past the age of 50. In other families, while there have been sporadic instances of cancer in the latter twenties, most of the cancers have developed in the fifth decade. The age, therefore, in which the adenoma becomes malignant, also, seems to be familial in nature. This observation has led us to recommend immediate or early total colectomy in the younger age families, while we have been willing to delay total colectomy somewhat in those who tend to develop cancer at a much later period. Again, these observations will be reported upon in extension at a later date.

Suffice it to say that when one encounters multiple polyps in a patient, he must realize that he is dealing with a lesion which sooner or later will eventuate into multiple carcinomas of the large bowel. Since sooner or later the entire colon will have to be removed, it seems to be a logical thing to remove the colon before the cancer develops.

This is radical surgery and requires considerable thought before such recommendation is made. In my opinion, it means a permanent ileostomy. While in many of these patients it is technically feasible to anastomose the ileum to the rectum low enough down so that the remnant of the rectum left behind can be easily visualized proctoscopically, it has been my experience that sooner or later this rectum will have to be removed. I have been impressed with the inability of the mucosa of these patients to stand a great deal of trauma. In several instances where a colostomy has been established, as we have staged the operation of total colectomy, during the period of only a few weeks while the patient was recovering from the previous operation we have noted the development of large adenomas on that portion of the mucosa attached to the abdominal wall.

Another predisposing factor in the production of adenomas—and, therefore, in the production of cancer of the large bowel—is chronic ulceration. One sees such polypoid overgrowth of mucous membrane in any type of ulceration of the large bowel which exists for a considerable length of time. The most classical cause, however, of such polypoid development is the so-called chronic idiopathic colitis of the ulcerative type. I cannot stress too strongly the tendency of this horrible type of disease eventuating into carcinoma.

No surgeon has had enough experience with total colectomy for chronic ulcerative colitis to speak with statistical assurance. In 98 instances in which total colectomy has been performed at the University Hospitals in Iowa we have encountered frank carcinoma in nine patients. This perhaps is a higher percentage than one generally anticipates.

Even though the percentage of patients with ulcerative colitis who subsequently develop cancer may not be as high as our experience has shown it to be, I should like to stress forcefully the fact that in the medical care of ulcerative colitis the subsidence of the acute symptoms does not necessarily exclude the development of cancer years later. Therefore, a patient who once has had ulcerative colitis is a potential candidate for cancer of the large bowel. The symptoms of this disease, therefore, must be explained to the patient and that patient must be under constant surveillance.

A final lesion of the large bowel which I should like to mention as related to carcinoma is that of diverticulitis. Diverticulosis of the sigmoid and transverse colon is a common finding in people beyond the age of 60. Diverticulitis, however, is not so common. The clinical picture of diverticulitis often can mimic that of adenocarcinoma considerably. When a chronic diverticulitis of the colon is diagnosed and it has been decided to hold surgery in abeyance, it must be remembered that cancer still may be present. I do not know whether the chronic ulceration that is so often associated with diverticulitis is related to the genesis of carcinoma of the large bowel. Again, the experience of any single surgeon has not been sufficient to solve the problem on a statistical basis. However, my own experience has been that the association of these two diseases has been frequent enough for me always to be disturbed when I encounter a focal area of diverticulitis; and although the patient may show considerable clinical improvement on medical care, I think it is important to repeat the x-ray examinations over a long period of time until one can exclude adenocarcinoma definitely.

It appears to me that we have advanced considably during the past 25 years in our understanding

and treatment of cancer of the large bowel. I think that we can anticipate even greater advances in the very near future. This is not idle wishing. If the knowledge which we already possess concerning the diagnosis and treatment of this lesion were completely disseminated and adequate facilities for diagnosis and care existed, much more could be accomplished.

A Review of Long Range Results of Massive Resection for So-Called Inoperable Carcinoma of the Abdomen

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Following the introduction of antisepsis and the continued development of anesthesiology, surgery during the latter part of the 19th century and early decades of this century established itself on an equal footing with internal medicine, the latter special field having dominated the healing art during the previous centuries. Numerous operative procedures were devised for the attack of a wide variety of neoplastic and inflammatory diseases. Techniques were evolved for the management of major and minor traumatisms. Operative surgery began to be regarded as having become crystallized about these many standard operations. In fact, in many quarters it was felt that operative surgery had reached the limits of its evolution and surgeons turned their attention to investigations of more or less fundamental physiological and biochemical phenomena associated with the surgical patient. Advances in bacteriology, nutrition, in physiological problems associated with surgical shock, the advent of the antibiotics—all of these contributed to making a major surgical procedure much less hazardous. With the increased safety under which surgical operations could be undertaken, it then became logical to inquire whether or not surgical operations themselves could be modified and extended. For example, the simple exteriorization operation for carcinoma of the colon a number of years ago was attended with a ten per cent mortality. If this could now be performed with a negligible mortality the question naturally arose whether exteriorization procedures were the operations of choice in regard to carcinomas of the colon. Indeed, it followed that the whole problem of the magnitude of surgical attack upon cancer had to be reevaluated. Three cases might be cited illustrating the magnitude to which a surgical operation may be carried with survival of the patient utilizing, of course, to the fullest extent all modern techniques for supportive measures of the patient undergoing operation:

Case 1. E. B., a 28-year-old white male, was operated upon for a large bulging mass in the left upper quadrant which had failed to regress under x-ray therapy and which apparently was the cause of extremely severe pain and discomfort every time the patient attempted to ingest food or liquids. At operation it was necessary to resect the tumor mass which was primary in the stomach by removing also half of the left lobe of the liver, the entire transverse colon, body and tail of the pancreas, spleen, omentum and areolar tissues in the upper posterior portion of the abdominal cavity. Adherent to the mass anteriorly was the fascia and musculature of the wall of the left upper quadrant and this also was resected. The operation was terminated by esophagojejunostomy, enteroenterostomy and double barrel colostomy, hepatic flexure to splenic flexure. Recovery from this massive resection was remarkably smooth and in a few days the patient enjoyed ingestion of limited quantities of liquids and food which gave him a great deal of satisfaction. He continued to do very well for a month and then suddenly developed widespread subcutaneous nodules, biopsy of one of which showed round cell sarcoma. By the end of the seventh week he had died and necropsy revealed widespread metastases involving practically all tissues and remaining organs of his body.

Case 2. F. M., a male aged 42 years. Roentgenograms showed two rounded masses in the left lung field typical in appearance of neoplastic metastases. In a series of films presented by the patient and taken over a period of two years, the presence of these masses and their slow growth was noted. He also complained of the continuous boring, severe upper abdominal pain with "high girdle" distribution (typical of pain produced by carcinoma of the body of the pancreas). No abdominal masses could be palpated. The patient having seen a number of physicians during the previous two years and ex-

periencing no relief from his pain stated in answer to our recommendation that he receive an abdominal exploration followed possibly by a second operation at which time the lung lesions would be removed, that he would undergo one operation but not two. Accordingly, the patient was prepared for laparotomy and through a high midline incision with left lateral extension the abdomen was opened, a fusiform swelling involving the body of the pancreas was found with no evidences of metastases elsewhere. Frozen section biopsy of the mass revealed fibrosarcoma and the body and tail of the pancreas with the spleen were resected. The abdomen was rapidly closed, the patient was redraped and, the patient still lying on his back, the fourth left rib was resected backward to the axillary line, the chest entered and a left total pneumonectomy performed. Both of these operations were, therefore, performed during a period of three hours with adequate supplies of blood, i.e., he received 1800 c.c., and shock did not develop at any time. Thus it was possible to do a subtotal pancreatectomy and splenectomy and a total left pneumonectomy at one sitting. He returned to work for a few months but died eventually of metastases one year and four months after the operation.

Case 3. A white male, aged 39 years, who because of abdominal pain was subjected to exploratory laparotomy in another institution. A primary carcinoma in the sigmoid was discovered with metastases that riddled the entire left lobe and with two metastatic foci in the right lobe of the liver. The abdomen was closed and the patient was told that he probably had about 60 to 90 days to live. Because of his strong desire to complete a certain business enterprise he stated that he was willing to do anything if he could be given about six months more of life. I operated upon him the middle of October 1948, and resected the primary lesion in the sigmoid performing an end-to-end anastomosis, resected an obviously metastatic gland in the mesentery corresponding to the site of the lesion. I then resected a small group of glands superior to the body of the pancreas which obviously were metastatic. Next, the entire left lobe of the liver which was riddled with metastases was excised and a resection of the solitary metastasis remaining in the right lobe was carried out. The second metastasis in the right lobe had been removed by the surgeon performing the previous operation in order to secure microscopic confirmation as to the nature of the lesion. Convalescence was essentially uneventful. It is now over three months since his operation, he is well, back at his desk at work carrying out all the duties which he had hoped to be able to carry out during the next six months. Interestingly enough he has gained 13 pounds in weight, has no pain and to all intents and purposes is living the type of life which he led about a year or so ago before the onset of symptoms.

Operations such as I have just described were performed in patients whose conditions were indeed desperate and if a certain amount of palliation was secured in that pain was relieved, prolonged survival was not anticipated in these patients. The question then arises in regard to the whole endeavor of radical surgery in what appears to be advanced abdominal cancer that conforms to the usual criteria of inoperability. If only very brief periods of relief are obtained, one might objectively argue the point whether or not such surgery is worthwhile. Would it not be possible to afford relief of pain by the judicious use of sedatives, careful adjustment of dietary regime, general activities and, if necessary, to perform ostomies or certain short-circuiting operations to obviate obstructions, chordotomies or lobotomies? I think that such arguments would indeed hold if more than just brief palliative relief from pain could not be obtained. Sufficient time, however, has now elapsed so that a more definite answer can be secured to the accomplishments of unusually radical procedures. Two years ago I collected a series of 100 consecutive radical resections performed for advanced abdominal cancer in the face of the usual criteria of inoperability. The first of these cases was performed some 12 years ago. Others were performed in the subsequent years. The purpose of this report, therefore, is to summarize briefly what has obtained in the way of prolonged survivals among these hundred patients.

(Lantern slides were shown demonstrating some of the operations and the operative specimens in patients who had survived for appreciable periods following radical operation for advanced cancer.)

Diagram 1 represents the fate of the hundred patients. Surgical mortality is indicated as 34 per cent; no patient died during the operation or in the operating room. Surgical mortality was defined as death within 30 days of the operation. In point of fact the average survival of patients in this group was six to seven days. In the next group of 17 patients there was thought to be no palliation and that the operation might well have not been performed as far as benefits to the patients are concerned. This group combined with the surgical mortality group equals 51 per cent of the whole series, roughly, half of the series. Therefore, in half the patients no benefit was obtained, they either died or were not relieved. In the remaining 49 per cent, however, it was felt that in 30 of the patients, or 30 per cent of the series, a very distinct palliation was obtained. The patients were markedly relieved from severe discomfort, obstruction, etc., and lived up to about

a year and one-half, some of them going back to their usual occupations at least part time. They all died of advancing and widespread metastatic disease. One of the things that impressed me was the fact that when widespread metastases did develop, the patients went down hill very suddenly and often died in a typhoid state, that is, relatively free from pain. The group that is of utmost interest, however, is the one of 19 patients, or 19 per cent in whom a prolonged survival was observed following radical massive resections for advanced abdominal cancer.

In Table I, seven patients are summarized who survived for periods ranging from two years and one month to five years. In all of these instances there was rather prompt recovery from operation and return to full time normal household or gainful occupation and a period that to all intents and purposes was characterized by a normal life in every respect. Attention is called to Patient No. 7, who died of a perforated stoma ulcer five years to the week after his operation and who was in effect a five-year cure since necropsy failed to reveal residual or metastatic tumor. His cause of death was entirely an intercurrent situation. Had we been much more radical in resecting the stomach it is possible that the stoma ulcer would not have developed and he would have continued to survive. At any rate the average survival in this group was for a period of three years and one month.

In Table II, are summarized the operations in 10 patients. These are all living and well today for periods ranging from almost five years to over 12 years. These can for practical purposes be classified as cures according to the usual definition, that is, five years survival without evidences of disease, except in one case, Case II, where after a period of six years and six months there is clinical evidence of recurrent disease in the region of the upper left posterior portion of the abdomen which was the former site of a massive adrenal cortical carcinoma. The average survival for this group of patients is six years and 10 months.

Reference has been made to 17 of the 19 patients in the long survival group. The two remaining patients proved not to have carcinoma when their radical operations had been completed and opportunity was afforded for study of the resected specimens. They both had had carcinoma proved by biopsy prior to radiation therapy. Complications of the latter in the presence of what prior to treatment was an advanced cancer led to the erroneous impression that cancer had recurred. The operations definitely established the fact that their disturbances were due to radiation reactions and burns and not to recurrent cancer. Inasmuch as they must be classified as radiation cures, they can not be included in this series of good results from radical surgery, therefore, they are subtracted from the group. The net result in the whole series of 100 cases is, therefore, 17 per cent. Seven of these patients lived for periods averaging three years and one month before disease recurred and was fatal. Ten of them, that is 10 per cent of the series, have obtained what for practical purposes is equivalent to a clinical cure. I do not think it is stretching the point to assume that if the operations had not been carried out, these patients, with their carcinomas in situ, would not have pursued such a prolonged course and would not have lived as comfortably or without further disturbances due to the obstructions some of them had. It is to be realized, of course, that simple short-circuiting operations above some types of carcinoma afford patients prolonged survival in comfort, but in these particular cases I do not believe that short-circuiting operations alone would have permitted the subsequent satisfactory courses which they all have exhibited.

At the onset of this work some years ago not a little skepticism and criticism was voiced regarding this type of surgery. This is easily understandable. On the other hand, sufficient time has now elapsed to permit of some impression as to what might be accomplished. It is shown that 10 per cent of the patients have been for practical purposes cured of what was considered advanced abdominal cancer. In a number of these instances previous exploratory laparotomies had been performed and the abdomen closed by competent surgeons because of the presence of the usual criteria of inoperability. A 10 per cent salvage rate is nothing to be inordinately proud of. However, this series of patients was selected not for lesions which might be favorable for surgical attack but for situations which were unfavorable for surgical attack and in a number of instances, as stated, had previously been subjected to surgical attack but there had been recurrences or extensions. In dealing with advanced visceral cancer a salvage rate of 10 per cent, while not a remarkable success, does represent in my opinion a pure gain inasmuch as these patients probably would not have been living today had not the procedures described been carried out. I am reminded of the remarks of one who reviewed the monograph referred to above and which appeared in 1947, where I described in some detail the 100 procedures that were carried out. This reviewer stated that he had seen some of these operations himself and that to him they represented veritable autopsies in the living and he added such procedures have no place in sound surgical practice. I can not help but often wonder what the state of mind of this colleague would be if he, himself, happened to be among the 10 per cent (prolonged survivors) which we discussed above.

As we all know, statistics compiled in order to afford objective impressions can be very misleading. Thus the mortality rate and the survival rate in the series which I have summarized apply only to this group of 100 patients. There is no reason to think that they could apply to a subsequent series of 100 patients or that they would apply in a series of 100 patients that might be developed by some other surgeon in another institution. The reasons for this are obvious and will not be discussed here. The important point is that by utilizing to the fullest extent all the measures for supportive treatment for the surgical patient that have been developed up to date and are being constantly improved, extensive surgical procedures can be carried out that not so many years ago would have been considered entirely fanciful and that not only can such patients be brought through the operation and through the immediate convalescent period but that they can be given some chance for prolonged survival in comfort and be permitted to live normally. With this in mind physicians, therefore, must in every case of so-called advanced cancer, deliberate thoroughly before pronouncing an absolutely fatal and hopeless prognosis, for while the chances for benefit in many cases might be extremely small, they nevertheless are there. An utterly defeatist attitude in the presence of what seems to be an advanced abdominal cancer is no longer justified.

Prospects in Cancer Control

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In ordering my thoughts in preparation for the remarks I am about to make to you, I was gradually led by certain considerations to wonder when the title of this speech was chosen and by whom: "Prospects in Cancer Control." Whoever he was, he has in some measure the gift of prophecy. For, since the State of the Union speech by the President, prospects for the future of cancer control, indeed for the future of all medical practice, have taken on added and deeper significance. You are neighbors of the President and it may be that this fact influences your political philosophy. I have no intention of engaging in controversy on my first visit to you, but I must say I can hardly discuss the future of cancer or of any other aspect of medical science without some reference to the possible role of the federal government.

I want to say at the outset that if there is a majority disposition on the part of the profession and on the part of the people they serve to maintain the status quo of medical practice, to preserve the dignity of individual responsibility based on free choice of a personal doctor-patient relationship, that position can be maintained with the help of the voluntary health agencies of our country. For example, the needs of poliomyelitis patients are being met today in a way which I understand is acceptable to doctors by and large. Now the difference between poliomyelitis and cancer or multiple sclerosis or mental illness is one of degree only so far as the economic aspects of disease are concerned.

I would like to remind you by way of prefacing what I have to say that nowhere in the world do the voluntary health agencies flourish as they do in this country. There are over 2,000 of them. They are supported for the most part generously and willingly by a public which can exercise, so far, free choice as to what agencies shall receive their gifts. I am sure that the present state of health in this country is in large measure due to the activities and to the stimulus of these voluntary health agencies. One can trace, I think, very clearly the growing effectiveness of the National Tuberculosis Association, in particular, in demonstrating to state legislators their responsibilities in tuberculosis control and can parallel the growth of that influence with the increasing controlability of tuberculosis.

There are two objectives in controlling cancer: the first is of course, the very obvious one: the discovery of a cure or a means of prevention. The second is perhaps not so easy to define because it consists of a number of interlocked factors. It is the effective use of methods we now have at hand. If we were to make no more progress—and you have heard today that we are making progress in clinical medicine—if we were to make no more progress in so far as our techniques of diagnosis and treatment are concerned, still by the maximum effective use of what we already have and know, we believe we could save over one-third of those who now die.

Now an analysis of the future can, I think, be made more meaningful and intelligent if we develop it from the point of view of the past and the present. I should like you to consider briefly the picture in 1913 when the American Cancer Society was founded. That is 36 years ago. Cancer stood eighth in the

list of causes of death, preempted by heart disease, tuberculosis, pneumonia, Bright's disease, diarrhea and enteritis, intracranial lesions of vascular origin and arteriosclerosis. And yet 71,000 per year were dying of it, or one in 18. What research there was was more of alchemy than science. There was one cancer hospital. There were no cancer clinics. There was no support of a program for cancer control by the federal government, and only one state recognized its responsibility thereto. There was no word of cancer which appeared in the media of public information for lay people. Nowhere was cancer a reportable disease in terms of morbidity. Biopsy was still a subject of controversy at medical meetings. Radiologists gingerly employed the newly discovered Roentgen rays. Radium cost $100,000 a gram, five times its present price. Surgery still bore the shreds of its frock-coat chrysalis. The operation for cure of cancer of the stomach was 30 years old. The hysterectomy which was then called radical but which we will have to modify now by some other term (perhaps radical prime) was then 16 years old. The operation for cure of cancer of the rectum was unknown. Tumors of the lung, esophagus, pancreas, and central nervous system were not yet surgical diseases. Anesthesia was limited to two or three agents of limited flexibility. Medical education was not standardized in any degree and diplomas awarded by diploma mills were recorded the same recognition as those of Hopkins and Harvard.

The intervening years, a period slightly in excess of a single generation, have seen advances of heroic proportions. If I may again digress to give you the general background so that you can appreciate the degree of progress which has been made, I would like to remind you that we are in the green years of medical discovery. Think how much we regard today as commonplace is less than 100 years old. It has been 108 years since Crawford Long demonstrated general anesthesia, 85 years since Mendel set down the laws of heredity, 83 years since Lister introduced antisepsis, 64 since Billroth successfully removed part of a cancerous stomach, 55 years since Roentgen gave x-rays to the world, 51 years since the Curies discovered radium, 49 years since the first hormone was isolated, 42 years since Freud applied what he could of science to the mind of man, 38 years since vitamins were described, 35 years since an impecunious Japanese succeeded in producing cancer at will for the first time on the ears of laboratory animals, 28 years since Banting discovered insulin, 18 years since Domaqk introduced the sulfonamides, 16 years since an entire lung was removed successfully for the treatment of cancer, 16 years since Joliot demonstrated artificial radioactivity, 13 years since the discovery of the molecular nature of the viruses, 10 years since penicillin as a drug was suggested by Flemming, nine years since Fermi set up the first atomic pile, five years since the pancreas was removed for cancer.

It is a fact from which we may all take heart that almost everything we know about cancer today, how to diagnose it, how to treat it, we have learned in the space of two generations.

Now, so far as the present is concerned, in respect of cancer research, let me say that there seems to be a very widespread belief among Americans that if you put enough money into something and mix it with the right amount of brains, the answer is bound to come out at the other end. That belief is born partly of our own remarkable technological advances and partly of the experiences of the recent war, and it may not be far from the truth, but let me say that there is an element in this formula which I believe is as important as money and brains and that is strategy. I believe that the voluntary health agencies which I hope will play an increasingly important role in the future of cancer in this country, have made a contribution in the way of strategy to the entire research program. In order to do this the American Cancer Society has called into being the Committee On Growth, a group now numbering 140 of the nation's leading scientists representing virtually every scientific discipline. These men meet at regular intervals in Washington or elsewhere and they consider unsolicited requests for grants-in-aid which come before them. They weigh them carefully and decide which, in the light of the limited funds available, are the most likely to bear fruit. They are recommended to the American Cancer Society and our role from then on is simply one of comptroller. But this committee has done more than simply weigh the merits of requests for grants-in-aid. The committee has attempted to analyze what Dr. Conant calls the "total scientific situation" and to define the avenues of research in greatest need of illumination, the avenues along which we may most profitably proceed in order to shorten the research task ahead. This is application of strategy, the bringing to bear on the subject of cancer, in a single organization, all of the scientific disciplines (and cancer is no longer the responsibility of the surgeon, nor of the radiologist, nor of the pathologist). There is practically no discipline in science which is not now called upon in our effort to solve the problem. These disciplines are represented in the Committee On Growth, and I believe that that committee is as devoid of partisanship as it is possible for a group of human beings to be.

I should like to tell you the extent of the present support of research in this country. From the American Cancer Society since 1945 you have heard Dr.

Nesselrode say we have had 81 fellowships supported; there have been 241 grants-in-aid; there have been 35 institutional grants, a type which is a new development and which I shall describe subsequently; and the total program has cost $7,815,000. This year alone, the Society will spent $3,200,000 in support of research. The federal government is spending annually $5,920,000. From state governments and foundations and from investigators' pockets, I estimate that we are spending $1,500,000; from the Atomic Energy Commission devoted to cancer alone $1,366,000; from the Damon Runyon Fund $1,300,434. This means a total of $13,286,434 last year alone in support of cancer research.

What have these researchers brought forward today? I have not the time, nor, I think, the competence, to go into them. I simply want to remind you of some of the things we know about cancer. We know that there are about 425 separate chemical compounds related basically of course which will produce cancer when applied topically or when administered in certain ways to laboratory animals. We know that there is a very striking similarity between the structural formulae of these known carcinogens and certain naturally occurring body secretions called the steroids, of which the sex hormones are perhaps the most familiar to you, and the entire relationship of hormones to cancer is of very recent development and one which I think is the most tantalizing at the present time. We know that there are three or four tumors in animals which are produced by viruses, those disease causing agents which behave like bacteria but which are too small to be seen. We are sure that they are there and recently some have been seen with the aid of newly developed instruments.

We know reasonably well what the genetic pattern in relation to the heritable factors now consists of as a result of 30 or 40 years of work by very careful laboratory workers. There has been brought to light recently a phenomenon which seems to touch on both the genetic and the virus side and that is the milk factor, something which seems to be present in the milk of mice of high cancer strains and which is passed on to their female offspring. Of course it is passed on to the males, too, but they naturally do not develop cancers spontaneously. The milk factor has been, it is alleged, identified as a virus. The field of isotopes has received a good deal of attention in the papers, perhaps more than it deserves from the point of view of the possible treatment of cancer, but certainly we can learn much of the basic processes of growth and body metabolism underlying malignant tumors through the use of isotopes.

Chemotherapy is based upon the search for drugs which will exert a specific, selective, toxic effect upon malignant tissue and leave normal tissue relatively unharmed. We haven't got what we are looking for but there are some interesting leads, for example the nitrogen mustards you have heard of, stilbamidine, urethane, colchicine (podophyllin) and now the folic acid antagonists.

Finally, we are working hard on the analysis of the protein nature of the nucleus and of possible relationship of enzyme systems which may interfere with the structure of the protein nucleus in cancer.

What about control? The answer to cancer will come from the laboratory ultimately. It may be five or 500 years in coming and until it does we must be about doing what we can with what we have in hand. The funds of the American Cancer Society for cancer control amount annually to $9,000,000; from the federal government comes $6,000,000. State governments provide about $2,500,000. The total budget for cancer control in this country then as contrasted to cancer research is $17,500,000. What does the program consist of? It consists of the attempt to educate 100,000,000 people about something they don't want to hear about. It consists of doctors training in medical schools, in their internships, in their postgraduate training, in residencies; and in an effort to keep practicing physicians abreast of our advancing frontier of knowledge in respect of cancer. There are in the country today 13 cancer hospitals; there are 434 cancer clinics; there are 74 cancer diagnostic clinics, a total of 521 facilities specifically designated for the diagnosis and/or treatment of cancer. There are about 230 cancer detection centers. There is a volunteer organization at work in this country which I think can do much to solve the problem of the terminal cancer patient. The cancer patient, by choice, or by necessity, usually spends his last days in his home. Thirty-four divisions of the Society operate loan closets supplying needed room equipment to people unable to pay for it. Forty-seven divisions have dressings units supplying fresh and sterile dressings to patients who need them in any quantity needed. Twenty-five divisions have facilities for transporting patients without cost to the doctor or to the hospital. This volunteer organization also provides other services, sitters, home care, occupational and recreational therapy, and assistance in the preparation of diets.

May I say a word about cancer detection centers? They are a point of controversy. The American Cancer Society didn't invent them. We do support them as we would support any new possibility of controlling cancer. I don't know whether they are good or bad. I am not sure that they interfere with the private practice of medicine. I do know this: that in this country in the cancer detection centers that are operating, 42 new cancers a month are being found in people who consider themselves to be

in good health. That may or may not be an achievement. It's a drop in the bucket; I'm sure of that.

In the collection of cancer statistics today, there is inadequate reporting of cancer deaths. The rate is 183 per 100,000 in New York state and it is 66 per 100,000 in South Carolina. This does not mean that your chances of getting cancer are less if you live in South Carolina, but rather that your chances of having your cancer found and properly treated are less. So far as morbidity is concerned only 25 states provide for the reporting of cancer under legal warrant, and in only two of these does it come close to being successful.

Now, as to the future. Does that research fund sound like enough? It is not! Suppose for example that we could be assured of discovering the causes of cancer and the means of preventing it if we were to spend $2,000,000,000 in research, which is what it cost to build one atomic bomb. At our present rate of spending, we would arrive at the answer to cancer in 142 years, but the secrets of cancer are certainly more elusive than the secrets of the atom. And we knew at the outset of the atomic project much more about the nucleus of the atom than we know today about the nucleus of the cell.

I do not believe that the answer to cancer will come in the future like a bolt from the blue, or that finding one piece will permit the others to be turned up very rapidly, although that is conceivable. I believe that cancer is many diseases and causes and there may be many treatments or many methods of prevention. In any case I am sure that our delineation of the problems and the answer will come by a process of slow eating away at the problem so that a future historian will never be able to say at what moment we had the answer in hand. It will gradually grow upon us. That's my idea and I may be proved wrong next week. I hope I will be!

How much money could be effectively spent now in the support of research? You have heard Dr. Nesselrode say that Mr. Adams said we couldn't spend much more than we are. That, however, was two years ago. We have turned out fellows since then, we have advanced the general area that we've been working since then, and I believe that $8,000,000 could be spent effectively next year over what we are spending at the present time.

We need to develop more cancer research centers. We have many small ones doing research which is nominal research but we need to develop more centers which have broad interests in cancer. I think we need to do this for this reason: we first of all need a proper spawning ground for young scientific minds. There just aren't enough top-flight laboratories to put trainees into. You've got to put them into laboratories a little lower down in the echelon of excellence, and put them to work, give them responsibility; as they become good, they will filter up by the process of selection which is well established and they will find their places. Moreover, in order to do top-flight research you've got to have a basic ground work of, shall we say, mediocre research going on. I do not feel, therefore, that we are being entirely fair in emphasizing the establishment of just a few research centers. On the other hand, we are being severely criticized for spending research funds according to a certain pattern. The pattern falls in the northeastern part of the United States. It falls around the northcentral states and it falls around San Francisco. People say to us, "This is favoritism. Those are the same areas of the country where the men on your Committee On Growth come from." Now it is not the fault of the poor volunteer health agency that scientists choose to group themselves in institutions the way they do. They are there. That's where we've got to go to get their advice and that's where we've got to go to get the work done. It is not our fault.

The future must see the development of more trained minds. And the need for financial subsidy during training and richer rewards during careers is very apparent to us. How this is to be done, I am not quite sure. Whether a voluntary health agency can undertake to do it, I doubt. There seems to be a need for a basic revision of our evaluation of men who are going to devote their lives to research. A man of great competence will come into a research laboratory and he will begin to learn something about a highly focused field of endeavor. If he is good, industry will come along and take him away at four times the salary he will earn in a university laboratory. If he is a doctor and we want him for teaching, he will be called away by the rewards of the private practice of medicine. This is the problem we are trying to face.

The prepared mind is essential to carry this investigation forward. On the wall of the student dormitory of Harvard University is the phrase of Pasteur: "In the realm of discovery chance favors the mind which is prepared." Now the stories of what has happened to prepared minds are, of course, numerous. Some of them are apocryphal. You are all familiar with the story of how Archimedes came upon the idea of specific gravity when he noticed the lightening of his own body when he dipped it into the bath and of how the young boy, James Watt, came upon the power of steam when in his mother's kitchen he saw the tea kettle lid being lifted off, and of Newton who lay musing one summer day in an apple orchard and by so casual an event as the dropping of an apple came upon a trend of thinking which led to the elaboration of a law of gravitational

force. The one I like best concerns Galileo, who, standing in a cathedral in Pisa, watched the long cathedral lamps swaying on their chains and by that stimulus was led to formulate the law of the pendulum from which came the validation of the Copoernican system and all we know today of the universe we live in. Now the point is that people had taken baths before Archimedes and apples had fallen before Newton, and Italians had watched the cathedral lamps swaying, but these people remained unmindful of the fact that they were being brushed by the winds of great mysteries. It took prepared minds to synthesize these simple events.

If we are to develop our man power to the fullest in the future I am sure that we must go beyond college and reach down into the high schools to set adolescent minds on the right road. One of my pet peeves is the methodology of teaching history, for example. History as it is taught today is simply a succession of political intrigues and military encounters. I think that science molds the course of history more potently than any of these. We want serenity, peace, contentment and the satisfaction of making our presence here worthwhile. We want time to live and love and read and listen and enjoy and marvel at the universe. These things science can give and is giving and yet, a history student can tell you the names of the bastard sons of the French kings but he can't tell you who invented the microscope. I believe that the saga of the development of nylon is infinitely more exciting and can be made so for young minds than the story of the Norman invasion.

So far as the future of research is concerned, let me conclude by saying that we stand on the shoulders of the scientists who have gone before. It is what I referred to before as the total scientific situation. There may come a breakthrough but I'm afraid it is unlikely because the course of scientific discovery is that of serendipity.

Horace Walpole many years ago read a story called "The Three Princes of Serendip," Serendip being a province on the island of Ceylon. These princes made a remarkable discovery. They would set out to go somewhere but they were constantly being beguiled by an attractive cove or a mountainside or a glen and if they went there and stayed instead of going where they started out to go they usually had a much better time. Now he applied this principle of finding a bypath richer than the path toward your original objective, serendipity. Incidentally he tried the word out on a literary friend and said, "What do you think it means?" His friend said, "I imagine it denotes that state of mind consisting of equal parts of serenity and stupidity." The course of scientific discovery is usually indirect. I like to think of it as a kind of Brownian particle progress—bouncing off this discovery, running up against this fact laid clean by a co-worker and steering into another direction.

That is the reason why I believe research of the future should be supported at an increasing rate on the basis of the mass or institutional grant rather than by grants-in-aid. You cannot put the blinders on a searchef for the truth... blinders which are inevitable if you hand him $4500 and say, "What are you going to do with it?" and he writes it down on a piece of paper, "I will do this with it." That is not the quickest way to get at the truth. The quickest way is to pick the right man, the man of integrity, the prepared mind, and to give him a large sum of money and say, "Go away and come back in three years and let's see what you've done with it." That is what the search for truth demands if we are to get at it in the shortest possible time and that is why we have set up a new formula for giving research funds which we call institutional grants... large grants, grants covering broad areas.

Now a word as to the future of cancer control. It is our objective to try to make every adult in this country aware of cancer's early warning signs and of the importance of doing something about it quickly. That is not easy. We've got to be a little bit bold about it. We are being criticized because we are frightening people about cancer but our critics are themselves divided into two camps: on the one side we have people saying, "Why you're frightening people so badly that they are afraid to go to the doctor." On the other side are the doctors who say, "Why, you're frightening people so badly that they are going to the doctor when they haven't got anything wrong with them." I don't believe that anything we produce, anything we write for the radio, anything that we make for a motion picture is sufficient to induce a serious neurosis. I think the neurosis is there to begin with and that if people are going to get neurotic about disease, if it isn't about cancer then it is going to be about heart disease, insanity, or pregnancy, or whatever else comes along to be the pin upon which they can hang their neuroses. And then, of course, people have been afraid of cancer for years and years before the cancer society ever came into being. If a person happens to feel that way because of a harrowing experience with a relative or friend the cancer society is more than likely to be blamed for it.

Now let me remind you that this is nothing new. "In the year 1734 suddenly the whole female population of Bensancon was overcome by a fear that they were suffering from cancer of the breast or might be so affected in the future. This followed the suggestion of a surgeon to the women of that city that they examine their breasts for lumps. The

sequel of this announcement was that all women examined their breasts so often and so long and squeezed them so much that a certain number really did develop lumps which were subsequently speedily removed by the surgeon with the greatest success." This is the account by Wolfe, of an epidemic of cancerophobia over 200 years ago. But note the successful outcome!

We are trying to develop more competent doctors. I say "we" meaning all of us; the government is trying to improve the teaching of cancer by liberal grants to medical schools; we are providing fellowships to enable young men of promise to develop added competence in the treatment of cancer and it does require added competence. We are trying to develop the right formula for interesting the general practitioner so that he will increase his index of suspicion and think of cancer first among the diagnostic possibilities in every patient who comes into his office. What about detection centers? They are doing a job as I have indicated. But as soon as every doctor is willing to take every patient seriously who comes into his office and who says "I'm all right but I'd like to be sure I haven't got cancer," and does what the patient expects him to do, does as complete an examination as he can within the limitations of his office, then every detection center in the country can close its doors as far as we're concerned.

Clinics? Well, if there are 434 and the American College of Surgeons says that one for every 50,000 of population is a good number, then we should have six times as many as we have and I can think of no state in the country which has done a more thorough job in establishing cancer facilities than your own state of Kansas.

We need to develop a formula within what is practical and reasonable for taking care of cancer patients who no longer can receive the benefits of surgery or irradiation therapy in a curative sense. We need to develop a plan whereby these patients can be put back in their homes and yet not completely dropped out of hospital census. They must be visited by doctors who know what they're about and by nurses who can give them about what is tantamount to good hospital nursing care. We think the formula for that has been established and that it will come into wide use in the years to come.

We need to know something about how many patients with cancer there are in the country and it can only be achieved by making cancer a reportable disease in every state. Whether it is done by law or on the basis of a voluntary registry doesn't matter—whichever is more agreeable to the doctors. We think we have the formula for that and every State Health Commissioner will be brought to Memphis in February in order that we can give him the formula and in the hope that he will carry it back and put it into use. We need to do something about the epidemiologic studies of cancer. We hear, for example, that smoke may cause cancer of the lung. Smoking cigarettes, or industrial smoke? We have the means; we have the technical competence now to lay that ghost and to find out whether it's true or whether it isn't. Is the atmosphere of Bridgeport, Connecticut, more cancerogenic than that of Santa Fe? Why don't Orthodox Jewish females get cancer of the cervix as much as the rest of the population? These are tantalizing problems in environmental cancer which could shorten the research task ahead if we could put them on the same dignified basis that we put laboratory research. We are coming out to Utah to see whether it's true that orthodox Mormons don't have cancer. We've heard they don't, and if they don't we'll find out why.

What are the dividends to be expected of this fullest possible use of what we know today? Well, they run something like this: the average patient with cancer of the larynx is hoarse for 5½ months before he goes to a doctor about it. We are curing about 30 per cent of cancer of the larynx in the best clinics today, but in selected series, patients with small tumors and who had been hoarse only a short time, the cure rate runs as high as 90 per cent. If a cancer of the rectum is as big as the end of your little finger and confined to the mucosa of the rectum, 80 per cent of the patients will survive for five years without disease. The overall cure rate of cancer of the rectum is, of course, about a quarter of that. Cancer of the cervix is curable in 70 per cent of the cases when the tumor is confined to the cervix. The overall rate is about 15 per cent in cancer of the breast; three out of four will live for five years without disease if their tumor is confined to the breast; the overall cure rate is about 40 per cent, and of the advanced cases the rate is 20 per cent.

I don't see much on the horizon of the future that is hopeful for cancer of the stomach or of the pancreas or of the liver, but there is a form of cancer which is said to be second in the list of causes of cancer deaths now and may actually be first; I refer to cancer of the lung, and there is something we can do about that because it is a surgical disease. It is curable. The man who was operated on in 1933 and had his lung removed and made history thereby is still practicing obstetrics in Pittsburgh, so you see it can be done. How do we get at early cases? By emphasizing the importance of mass chest x-rays. They are as vital as tuberculosis case-finding studies. Tuberculosis is interested largely in young people because that's where tuberculosis occurs. We are interested in old people, 45 and over, because that's

where cancer occurs. I think that our program of chest examinations should be at least as vigorous as that of the tuberculosis association.

Now there is one strike against us and it is a serious one. We can do everything I've said and I'm afraid the death rate from cancer will increase in spite of us and it is for this reason: that as a population we are aging so very rapidly. In the year 1900, there were 13,000,000 people in this country 45 or over. Today there are 39,000,000 people 45 and over, an increase of three fold. This same Horace Walpole that I'm so fond of said some 150 years ago: "About the time I die or a little after it will be discovered how men may live forever." A very clever poet answered him not long ago. She said:

Horace, be comforted to die,
One century has measured by
And half the next
Since it was true
The temporal state eluded you.

Now as I read your pensive letter
I wish myself that times were better,
That I might boast how men contrive
As you foretold, to stay alive.

By now we should possess the key
To fleshly immortality
And, if we wanted to endeavor
To live forever and forever.

This to my infinite regret
Is not a custom with us yet.
I write you Horace for good cheer,
Life is about as usual here!

Now there is room for everybody in the future in this effort to control cancer. There is a job for the government to do. There is a job for the voluntary health agency to do. There's a job for every doctor to do. I believe that we can work together if we will sit down and arrive at a reasonable program. We already have a good working relationship with the National Cancer Institute officials, and for practical purposes, we divide our provinces. In effect, we say, "We can educate lay people better than you can, Government, but you may have to subsidize medical education. Nobody else has the money to do it. Doctors take our efforts to keep them abreast of our advancing knowledge a little more kindly than they'll take yours, therefore we do that. You give more money in support of research and see that you do it without any political controls."

If I may become personal, let me say that you must not feel that because you're not looking through a microscope and because you're not trying to extract an etiocholenolone from the urine of a patient with cancer that you haven't got a contribution to make. We all have according to our ability. It may be great, it may be small, but it is there. When I think of that I am reminded always of what an old Quaker lady said when I went to college. I went to a Quaker college and we were dragged to meeting once a week; we didn't like it then, but I heard some very wise things said. She was a very old lady and she told us how when she was young her father had taken her into country which was then quite wild, into the Grand Canyon. They had gone farther than they knew and as they turned to come back their horses were dry and desperately in need of water. As they tried to indicate to the animals in what direction they thought water was, the horses refused to move but stood still pawing the ground. There beneath what appeared to be dry sand and rubble, eight inches down, they came on water. Her moral was that if we will look for the freshets of the spirit beneath the rubble of the routine of our daily lives, we'll find there things that are useful and which are intimations of great achievements.

The Diagnosis of the Leukemias and the Malignant Lymphomas

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I. The Leukemias

Leukemia may be described as an invariably fatal disease of unknown origin characterized by abnormal, unbridled proliferation of leukocytes, principally the precursor forms, in their usual sites of development and in various other body tissues as well. As a rule, the process is reflected by characteristic changes in the number and morphologic characteristics of leukocytes in the peripheral blood stream. In a considerable percentage of clinically and pathologically identical cases of leukemia, the peripheral leukocyte count is found to be normal or subnormal. To classify such cases, the inconsistent term "aleukemic leukemia" is generally employed. Some authorities prefer the designation "subleukemic leukemia," which has the distinction of inaccuracy in a different sense. "Leukopenic leukemia" almost always describes the situation more satisfactorily but is less commonly applied.

Classification.—The leukemias are conveniently labeled in recognition of the type of leukocyte primarily involved. While interesting subvarieties occur, to the pleasure of the morphologic hematologist, the great majority of cases are satisfactorily classified as myelogenous, lymphatic or monocytic. The degree of immaturity of the leukemic cells, coupled with clinical considerations, permits further separation of the leukemias into acute, subacute and chronic forms.

The relative incidence of the various types of leukemia is difficult to determine because of differences in terminology employed by different observers and because of the difficulty all have experienced in sorting out some of the "stem cell" types.

Age Incidence.—Leukemia of all varieties occurs at all ages. During childhood and through the early twenties, the great majority of cases are of the acute variety. Chronic myelogenous leukemia is the most common type during the third and fourth decades, while chronic lymphocytic leukemia is the predominant type after 50 years of age. Monocytic leukemia, which is more often acute than chronic, occurs most often in the middle-aged group.

Diagnosis. 1. Clinical Manifestations.—Clinical manifestations of acute and chronic leukemia are too numerous and variable to permit detailed consideration at this time. However, the signs and symptoms provoked by the different morphologic varieties are sufficiently similar to allow a general consideration of the two principal clinical types, acute and chronic (Table 1).

Table 1

Leukemia: Clinical Manifestations

Chronic	*Acute*
1. Enlarging hematopoietic structures	1. Decreased production of normal blood cells
2. Infiltration of other organs and tissues	2. Increased catabolic activity
3. Decreased production of normal blood cells	3. Enlarging hematopoietic structures
4. Increased catabolic activity	4. Infiltration of other organs and tissues

(a) Chronic Leukemia.—In chronic leukemia, the onset is usually insidious and the course is slowly progressive. Many cases are discovered accidentally during routine examinations or during studies carried out for unrelated conditions. Observation of such cases indicates that a period of two or three years may elapse after the discovery of an abnormal blood picture before significant symptoms develop.

(1) Enlarging Hematopoietic Structures.—These most often provoke the symptoms leading the person who has chronic leukemia to visit his physician. A sense of fullness in the left upper quadrant of the abdomen or attacks of pain in the same region may call attention to the presence of splenomegaly. In chronic myelogenous leukemia, the spleen may attain staggering proportions. Splenomegaly is also the rule in chronic lymphatic leukemia but is usually only moderate in degree. Conversely, lymphadenopathy is often striking in chronic lymphatic leukemia but is infrequently observed in chronic myelogenous leukemia. Enlarged mediastinal nodes may, of course, provoke a variety of symptoms.

(2) Leukemic Infiltrations of Other Organs.—While widespread infiltration of the various organs and tissues is common to leukemias of the various types from the pathologic point of view, clinically significant involvement of the skin and the gastrointestinal and respiratory systems occurs with greater frequency in chronic lymphatic leukemia than in chronic myelogenous leukemia. Cutaneous involvement in the latter is a notable serious prognostic sign, but occurs relatively early in a considerable number of cases of Schilling's monocytic leukemia.

(3) Disturbance of Production of Normal Blood Cells.—This is thought to result from "crowding out" of normal hematopoietic elements by leukemic cells in the bone marrow. In chronic leukemias the symptoms of anemia usually appear during the course of the disease. Purpura, resulting from thrombocytopenia, usually is a late development if it appears at all.

(4) Increased Catabolic Activity.—This, as evidenced by loss of weight, sweating, an elevated basal metabolic rate or nervousness, may be manifest in chronic forms of leukemia but these symptoms are most prominent in the terminal phases. Fever is relatively rare in chronic leukemia; its appearance often indicates an acute transformation of the process.

(b) Acute Leukemia.—This is characterized by a fairly acute onset, often suggesting an infectious disease, with a precipitous course to death within a period of weeks or months.

(1) Disturbance of Production of Normal Cellular Elements.—This causes severe, progressive anemia, hemorrhagic phenomena or lesions resulting from impairment of normal defense mechanisms (noma, and so forth) and is often responsible for the initial symptoms.

(2) Increased Catabolic Activity.—This produces fever, prostration and malaise, and is a common early development.

(3) Enlarging Hematopoietic Structures.—These are responsible for symptoms relatively infrequently in cases of acute leukemia. The spleen, when palpable, is usually only slightly enlarged. However, it may be considerably enlarged in some cases of acute lymphatic leukemia. Lymph nodular enlargement is not often conspicuous except in occasional cases of acute monocytic leukemia.

(4) Infiltration of Other Tissues.—This is apparent clinically less often in acute than in chronic forms of leukemia. Swelling and ulceration of the gums often develop in acute leukemia, particularly the monocytic form. Involvement of bony structures, with bone and joint pain, may suggest the diagnosis of rheumatic fever or osteomyelitis.

(c) Subacute Leukemia.—A subacute category has been utilized to include cases with intermediate clinical manifestations. Usually they more closely resemble the acute forms than the chronic. Cases in which the patients survive six to twelve months after the onset of symptoms have been arbitrarily regarded as subacute by some authorities.

It should be emphasized that the clinical course of a case of leukemia is subject to extreme and unpredictable individual variation. Approximately one third of chronic cases assume the clinical characteristics of the acute variety in the terminal stage of the disease.

2. Hematologic Findings.—The principal features of the blood picture encountered in the usual case of acute or chronic leukemia are summarized in Table 2. Time will not allow a detailed morphologic discussion, but accurate classification of the process is highly desirable from the standpoint of therapy and prognosis.

(a) Leukocyte Count.—The total count is highly variable in all types. The level of the leukocyte count does not necessarily parallel the clinical picture. In the same case, the count may range from leukopenic to extremely high levels. Aleukemia, or leukopenic leukemia, constitutes as many as 50 per cent of cases of lymphatic origin, including particularly the acute forms of the disease. It is less common in the myelogenous variety.

(b) Differential Count.—The basophilic leukocytes are commonly increased in chronic myelogenous leukemia. The percentage of very immature forms or stem cells usually is less than five per cent in chronic leukemia. On the other hand, the percentage of stem cells in acute leukemia is usually much greater and may be 90 per cent or more. In acute leukemia of the myelogenous type, reddish rodlike cytoplasmic inclusions called "Auer bodies" are frequently seen. Occasionally the picture defies differentiation into a specific type and must be classed as a stem-cell leukemia. The type may, however, be suggested by the character of the accompanying cells.

Table 2

Leukemia: Hematologic Findings

	Chronic	*Acute*
Leukocytes	Leukopenic to very high levels. Usually 200,000 to 300,000	Often leukopenic Rarely exceeds 100,000
Differential	Disturbed in favor of cell type involved. Immature forms	Greater percentage of blast forms. Auer bodies
Erythrocytes	Mild to moderate anemia common, varying with stages of disease	Moderate to severe anemia characteristic
Platelets	Not remarkably altered. Thrombocytopenia often develops late	Thrombocytopenia in majority of cases

(c) Erythrocyte Count.—A normocytic, normochromic anemia, commonly attributed to infiltration of the marrow by leukemic cells, eventually appears in almost all leukemias. The process may be macrocytic, or, rarely, hemolytic in character. Normoblasts are sometimes present in the peripheral blood in chronic myelogenous leukemia.

(d) Platelet Count.—Thrombocytopenia is a poor prognostic sign in chronic forms. It is more commonly encountered in early cases of chronic lymphatic leukemia than of chronic myelogenous leukemia. The bleeding tendency in leukemia probably results from thrombocytopenia plus leukemic infiltration of vessel walls. It should be emphasized that while attention is likely to be drawn to the abnormalities in the leukocytes in cases of leukemia, anemia and thrombocytopenia are almost constant accompaniments in the well-established chronic forms and in most acute forms of the disease.

(e) Sternal Marrow.—Improvements in the technic of aspiration of sternal bone marrow now allow almost "routine" use of this procedure. Study of sternal marrow specimens is not necessary to establish the diagnosis of leukemia when the disease is manifested by the classic hematologic and clinical signs noted previously.

The bone marrow picture in chronic myelogenous leukemia is nonspecific but is highlighted by hyperplasia and a moderate degree of left shift in the myeloid line. In chronic lymphatic leukemia more than 40 per cent of the nucleated forms are usually lymphocytes. In Schilling types of monocytic leukemia the majority of the nucleated cells in the marrow are monocytes, immature monocytes or monoblasts. In acute leukemia the marrow is packed with primitive cells. "Dry taps" are common with the needle aspiration technic in this type of case and trephining may be necessary to provide a satisfactory specimen.

Differential Diagnosis.—The diagnosis of leukemia is quite simple when the classic hematologic and clinical findings can be demonstrated. While leukemia may simulate many other disease processes in its clinical manifestations, a careful study of the blood and bone marrow usually either establishes or excludes the possibility of such a diagnosis.

Leukemia is most frequently overlooked when encountered in the aleukemic phase. Aleukemic leukemia presents all the clinical features of classic forms of the disease but the leukocytes of the peripheral blood are normal or subnormal in number. This type of leukemia is more common in lymphatic leukemia, particularly of the acute variety, and is relatively infrequently encountered in cases of myelogenous leukemia. In such cases the differential pattern is consistently abnormal, but immature forms may be overlooked unless a painstaking search is carried out.

Chronic forms of aleukemic leukemia are commonly mistaken for cases of aplastic or pernicious anemia, Banti's disease or malignant lymphoma. The hematologist sees many cases in which aleukemic leukemia has been vigorously and fruitlessly treated with liver extract, folic acid, iron or a combination of these agents in the belief that they represented unusual, refractory forms of anemia. Acute forms of aleukemic leukemia may simulate idiopathic thrombocytopenic purpura or agranulocytosis in clinical manifestations.

However, careful study of the peripheral blood usually provides clues to the correct diagnosis and the sternal bone marrow presents the characteristic picture of leukemia as noted previously.

Leukemoid Reactions.—An erroneous diagnosis of leukemia is most often made in the presence of conditions which provoke leukemia-like, or leukemoid, changes in the peripheral blood picture. These reactions are stimulated by a variety of circumstances and diseases. For the most part, clinical similarity to leukemia is confined to the blood picture and adequate clinical observation permits differential diagnosis.

Leukemoid reactions of the myeloid type may result from the bone marrow stimulation which is a normal response to any pyogenic infection. A similar reaction may follow burns, chemical poisoning, diabetic acidosis or metastatic involvement of the bone marrow. Severe leukocytosis may accompany conditions in which an acute need for red blood cells develops. The marrow is stimulated to increased activity and as the red blood cells are poured out, white blood cells, some of them immature, are also released. This may occur in any acute hemolytic process, in pernicious anemia in crisis, following severe hemorrhage, and in some cases of polycythemia vera. In instances in which a great need for red blood cells exists over a long period, and, for one reason or another, the bone marrow is unable to meet these needs, ectopic blood formation in other organs develops. This commonly occurs in the spleen, the liver, and sometimes in the kidneys but may involve other structures. In osteosclerosis or marble bone disease, osteofibrosis, chronic hemolytic anemia, and in cases of prolonged untreated pernicious anemia, metaplastic foci of blood formation develop. Immature blood cells theoretically enter the circulation in this group of cases because of the fact that in these extramedullary foci of blood formation, the release mechanism for the leukocytes and the erythrocytes is defective and immature cells are allowed to enter the circulation along with the mature forms.

Leukemoid reactions of the lymphatic variety are

less common but sometimes more confusing. These reactions occur most often in children. It is important to remember that in children, the bone marrow reacts more readily and more vigorously to various stimuli than does the bone marrow of adults and that leukemoid reactions of all varieties are more common in the younger age group. Infectious mononucleosis may produce a picture similar to that of leukemia, but is accompanied by diagnostically specific serologic and morphologic changes in the blood. Infectious mononucleosis follows a benign course and neither anemia nor thrombocytopenia accompanies this condition. Pertussis may provoke lymphocytosis of extreme degree. The differential diagnosis depends upon recognition of the underlying disease. Occasionally lymphocytosis is seen in brucellosis, tuberculosis which is active, and congenital and secondary forms of syphilis. These are relatively rare. A confusing monocytosis has been noted occasionally in cases of subacute bacterial endocarditis.

The fairly constant association of anemia and thrombocytopenia with leukemia is a helpful point to remember. If doubt remains, study of the sternal marrow usually excludes the possibility of leukemia.

Finally, it should be remembered that leukemoid reactions are particularly common in association with infectious diseases of infancy and childhood whereas leukemia happily remains a rare disease. Consequently, the diagnosis should be made only after careful consideration of all factors.

II. Malignant Lymphomas

This term includes a group of diseases characterized by progressive enlargement of lymphoid tissue, simultaneous or subsequent involvement of other tissues and organs, and uniformly fatal termination.

The diverse manifestations and variable clinical courses provoked by these disorders are notorious and, as with the leukemias, have made accurate prognosis difficult and results of therapeutic efforts difficult to assay. In recent years, the detailed studies of Jackson and Parker[1-4] and of Gall and Mallory[5] have provided pathologic classifications which appear to have considerable clinical usefulness, although the validity of these attempts at sharper separation of these diseases has been contested[6]. While the pathologic picture in the individual case seems to remain much the same over periods of months or years in the majority of cases, instances of inconstancy and overlapping of cell types must be anticipated. It remains difficult or impossible to distinguish the various types of lymphoma on the basis of clinical features alone.

Lymphosarcoma.—By Kundrat's[7] definition, lymphosarcoma has been regarded as a process of unicentric origin, eventually extending metastatically by the lymphatics, blood vessels or tissue spaces to adjacent or distant regions. However, some cases closely resemble lymphatic leukemia, a process of presumably multicentric origin, from the clinical standpoint, including the development of a leukemic blood picture. One's therapeutic strategy must be influenced by consideration of factors indicating a process of one or the other of these extremes.

The following varieties of lymphosarcoma may be considered[5] (Table 3):

Table 3
Lymphosarcoma

Stem-cell variety	Reticulum-cell type
Clasmatocytic	
Lymphoblastic	Forms of lymphatic
Lymphocytic	leukemia?
Giant follicular	

1. Reticulum-Cell Sarcoma. (a) The Undifferentiated Stem-Cell Variety.—The average age at onset is later than in Hodgkin's disease. Enlargement of superficial nodes is the commonest early manifestation. Abdominal symptoms, often signifying gastro-intestinal involvement, were the presenting complaint in 17.5 per cent of Sugarbaker and Craver's 196 cases[8]. Involvement of the upper part of the respiratory passages (nasopharynx, tonsils) often occurs as the first manifestation of the disease. Gastro-intestinal and upper respiratory sites comprise the majority of instances of primary extranodal disease. Splenomegaly is demonstrable in approximately 21 per cent. Systemic symptoms (anemia, loss of weight and fever) occur relatively late in comparison with the same symptoms in Hodgkin's disease. The average duration of life is 1.7 years (three per cent ten-year survivals). The prognosis is better if the process begins in the upper part of the respiratory tract or if only one or two regions are involved when treatment is instituted.

(b) Clasmatocytic Variety.—The predominant cell seems relatively well differentiated in this type and exhibits phagocytic ability, simulating normal clasmatocytes or monocytes. Clinically, this form of the disease closely resembles the stem-cell variety. However, monocytosis occurred in 22 per cent and a leukemic blood picture in five per cent of Gall and Mallory's series[5]. There is little from a clinical standpoint to distinguish the latter from Schilling's histiomonocytic leukemia.

2. Lymphoblastic or Lymphocytic Lymphosarcoma.—Some authorities feel that these cases are pathologically indistinguishable from lymphatic leukemia[9]. A leukemia-like blood picture has been observed during the course of 30 to 40 per cent of cases

of this type of lymphosarcoma and under such circumstances differentiation from lymphatic leukemia is indeed difficult. Isaacs[10], supported by Sturgis[11], expressed the belief that "lymphosarcoma leukemia" is a clinical entity and that characteristic cells are demonstrable in the circulating blood in such cases regardless of the total leukocyte count. Sturgis found the life expectancy of his 70 patients to be approximately one half that of the average patient who has chronic lymphatic leukemia (60 months).

3. Follicular Lymphoma.—This constitutes a fairly distinct pathologic and clinical entity, although it seems closely related to the lymphocytic and lymphoblastic forms of lymphoma and the terminal pathologic picture may be identical. The average age at the onset of symptoms is about 50 years. The average life expectancy (six years) is considerably better than that for the other members of the lymphosarcoma group. The process appears to be more closely confined to the lymphoid tissues in the early stages, systemic manifestations are less striking and the response to treatment is more gratifying. The spleen is palpable in approximately 60 per cent of cases at some time during the course of the disease. The retroperitoneal nodes are commonly involved and the development of chylous ascites is not unusual[12].

Hodgkin's Disease.—This has been separated into three principal types by Jackson and Parker[1-4] (Table 4).

Table 4

Hodgkin's Disease

Paragranuloma—relatively benign process.
Cervical adenopathy often only symptom.
Long survival. 20% progress to granuloma.

Granuloma—classic type (90%). Slowly progressive course with prominent nodal involvement, early systemic manifestations, and variable local symptoms.

Sarcoma—behaves as true neoplasm, with symptoms suggesting rapidly progressing, malignant disease of internal organs. Superficial adenopathy absent in 50%.

1. Paragranuloma.—The paragranulomatous form bears little resemblance to usual neoplasms either in its histologic picture or in its clinical course. Cervical or axillary adenopathy may be the only clinical or pathologic manifestation of the disease. Most patients have survived for long periods after surgical extirpation of, or aggressive roentgen radiation administered to, the involved nodes, but approximately 20 per cent have progressed to develop the characteristics of the granulomatous variety.

2. Granuloma.—The granulomatous type, with an average life expectancy of two to three years, is the classic variety of Hodgkin's disease. The process may and does involve any organ in the body containing lymphoid or reticulo-endothelial tissue. Consequently, enlargement of superficial nodes may be only external evidence of established disease in the interior. Systemic reaction, in the form of fever, loss of weight, weakness or malaise, usually develops relatively early, followed or accompanied by various evidences of local distress resulting from the pressure of enlarging nodes or organ infiltrations. Intrathoracic, cutaneous and osseous involvement is particularly common. While patients frequently complain of abdominal pain this seems to result from retroperitoneal more often than actual gastro-intestinal involvement. Eosinophilia occurs at some time in about 20 per cent of cases and monocytosis is frequently observed. Anemia develops much earlier than in cases of lymphosarcoma.

3. Sarcoma.—Hodgkin's sarcoma is a highly malignant process from the pathologic point of view, which presents symptoms suggesting involvement of internal organs (retroperitoneal nodes, gastro-intestinal tract and respiratory system commonly involved) accompanied by the systemic evidences of a rapidly progressing malignant disease. Significant superficial lymphadenopathy may be present in only 50 per cent of cases. This type of Hodgkin's disease occurs in an older age group (sixth and seventh decades) and carries a life expectancy of about six months although the original response to treatment may seem encouraging.

Differential Diagnosis.—While malignant lymphoma may simulate a great variety of diseases, the following conditions most often cause diagnostic difficulty.

1. Lymphadenopathy Secondary to Local Inflammatory Disease.—This should subside as the primary process clears up. If enlargement of nodes persists for more than two to three weeks without obvious explanation, biopsy should be performed.

2. Leukemia.—In the forms of lymphoma presenting a leukemic phase differentiation may be extremely difficult. Usually, careful study of the blood and, when necessary, the bone marrow, establishes the diagnosis of leukemia.

3. Tuberculous Adenopathy.—If acute in development, tuberculous glands may remain discrete and movable. Tuberculosis more often involves the submaxillary and anterior cervical nodes while Hodgkin's disease may often affect the posterior cervical chain. The demonstration of calcification in enlarged lymph nodes favors the diagnosis of tuberculosis.

4. Metastatic Carcinoma.—Biopsy is usually necessary for differentiation if the site of the primary lesion is obscure. Nasopharyngeal tumors are often

small and easily overlooked and the first symptom of such disease may be the development of marked cervical adenopathy.

5. Syphilis.—The nodal enlargement of syphilis is rarely marked. If a primary lesion is not apparent, serologic studies provide the correct diagnosis.

6. Infectious Mononucleosis.—This has a benign clinical course and occurs in younger age groups. Diagnostic serologic and morphologic changes are demonstrable in the blood.

7. Boeck's Sarcoid.—This condition may very nearly duplicate Hodgkin's disease from the clinical viewpoint. However, the lymphadenopathy rarely attains large proportions and often involves the preauricular and postauricular, submental, submaxillary and epitrochlear groups. Paratracheal adenopathy is characteristic. The uveal tract is frequently involved and small "punched-out" lesions are often demonstrable on roentgenographic examination of the bones of the hands and feet. The serum protein level is usually high and the tuberculin skin reaction is negative.

8. Other Conditions.—Unless nodes or tissue accessible to biopsy are involved, it may be practically impossible to differentiate lymphoma from other conditions causing mediastinal tumor, abdominal tumor or bony lesions. In most instances, an accessible lymph node can be uncovered sooner or later. The so-called therapeutic test with roentgen therapy is sometimes carried out but should be considered only as a last resort.

9. Disseminated Lupus Erythematosus.—This provides a picture sometimes grossly similar to that of malignant lymphoma but the degree of lymphadenopathy is seldom marked and evidence of cardiac or renal involvement is usually apparent. Recently Hargraves and his associates[13] have demonstrated the existence of a specific cellular element in the bone marrow in clinically "active" cases of disseminated lupus erythematosus.

Diagnosis.—It remains established that the positive diagnosis finally depends on the demonstration of the characteristic histopathologic picture in involved lymphoid or other tissue.

Material for study is most commonly and satisfactorily obtained by excision of an involved superficial node. Cutaneous lesions may also provide satisfactory material for microscopic study.

Aspiration biopsy of involved enlarged hematopoietic structures, the liver and other organs and tissues has been carried out with occasionally satisfactory results, but the hazards attached to such procedures may be appreciable and the material obtained is often unsatisfactory for definite diagnosis.

In view of the very high percentage of cases of Hodgkin's disease in which bone and bone marrow lesions are observed at necropsy and the similar though less frequent occurrence of bony lesions in other members of the malignant lymphoma group it was hoped that study of aspirated bone marrow material would provide another simple means of establishing a positive diagnosis of malignant lymphoma. While material of diagnostic value is obtained in rare instances by this method, the findings in the overwhelming majority of instances are disappointingly nonspecific. The usually focal character of the process accounts for this difficulty and the employment of multiple sites of aspiration might result in a higher percentage of positive results[14].

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Fight Cancer

Diagnosis and Treatment of Endometrial Cancer

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Probably the greatest step forward in the diagnosis of endometrial cancer is universal recognition of the established fact that this type of malignancy can occur during the active menstrual life of an individual and need not necessarily cause irregular menstrual bleeding.

This recognition was influenced by the work of Randall in his study of a large series of endometrial carcinoma cases in which he tried to divide the cases into first, postmenopausal bleeding; second, metrorrhagia; and third, no apparent alteration in the menstrual period except an increased flow. His conclusion was that the woman 40 years of age or over who has an alteration of her menstrual flow, either prolonged or increased in amount, has a higher incidence of malignant disease of the endometrium by at least 10 per cent. This was so in the cases that were complicated by benign disease, myomata, etc. Therefore, we began to recognize the fact that when the menstrual flow was altered we had better investigate. We had always admitted that in all probability postmenopausal bleeding was indicative of malignant disease, or that irregular bleeding occurring in between the periods of regular menstrual flow was also indicative of disease.

The economic situation, of course, forbids that all of these patients be hospitalized for curettage. We must very carefully screen them clinically in order not to overlook the group with the 10 per cent incidence where the normal incidence runs somewhere in the neighborhood of three per cent. This brings up the question of other diagnostic procedures such as the smear, the cytologic study, or aspiration curettage. I have always hesitated to admit as positive proof a negative aspiration curettage, the so-called office or clinic procedure, for fear that the curettement had not removed all areas of the endometrium. With such a fine instrument as a Novak or a Randall curette, I can conceive that it is very possible to miss entirely the site of malignancy.

We, therefore, have compromised by admitting these patients into the hospital in the morning and, under sodium pentothal anesthesia, performed a thorough curettage and sent them home by three or four o'clock the same afternoon. In this way it is possible to handle a large number of patients without clogging up the beds in the hospital. This is a relatively safe procedure because it has been done over a period of some 10 years without any complication and is certainly much more reliable than any other form of curettage, or any diagnostic substitution that I have mentioned.

The Papanicolaou technique of cytologic study certainly has its place in a well developed and well staffed clinic. It cannot be used as a generalized screening process for all women 40 years or over because, as you were told yesterday, it would be impossible to have a sufficient number of trained cytologists to even screen the slides before they are passed on to the pathologist for an opinion. Therefore, this technique is used in those patients where the curettage is negative and where the answer to the increased menstrual flow or the irregular bleeding is not forthcoming. In such cases, the number of which is relatively small, I believe that this procedure has a definite place and is an excellent addition to our diagnostic acumen.

By performing these curettages we are beginning to uncover in the endometrium changes which are similar to the pre-invasive carcinomas now being described and recognized in the cervix. Novak in his recent publication has demonstrated changes in the adenomatous structure of the endometrium which he interprets as pre-invasive carcinoma of that tissue, and I believe sincerely that before long we are going to have sufficient experience to begin to talk about pre-invasive carcinoma of the endometrium.

With the diagnosis in our hands, how are we going to proceed in the treatment of this condition? About 1935 we published a procedure for the radiologic treatment of endometrial carcinoma, developed primarily for those patients who were not considered surgical risks, having such conditions as thoracic complication, cardiac complication, severe diabetes, or other diseases contraindicating operation. From a study of the literature it is shown that about 20 per cent of patients having proven endometrial carcinoma treated by irradiation survived over the five-year period.

If adenocarcinoma of the endometrium were diagnosed early, then properly and thoroughly treated, it might be possible to duplicate the same end results being obtained in the treatment of squamous carcinoma of the cervix. Such a radiological procedure has been carried out for a time in a group of fundal malignancies and the uterus was surgically removed in order to obtain the specimens for pathological study. Figures 1 to 6 demonstrate our clinical idea as to the extent of disease and the grouping of fundal or endometrial carcinoma.

Figure 1 is an extremely early lesion where the cancer has not as yet broken through into the uterine cavity, a condition which oftentimes exists and which we are likely to miss with the curette. The uterus has not been altered as to size or shape, and there is no alteration in its consistency. This we classify as a clinical Group I carcinoma.

Figure 2 shows that the lesion has broken through the uterine wall and is showing distinct growth tendencies. It is infiltrating as well as proliferating. There is no question but that there is further migration of cellular elements, and this is called a clinical Group II.

Figure 3 demonstrates another Group II lesion, traveling down along the endometrial surface, invading into the myometrium but still causing no alteration in the size of the uterus itself. Now, you may ask me how you can group these cases clinically without visualizing the extent of the disease. This is based on the findings of the clinical examination, the bimanual examination which determines the size, the mobility and the consistency of the uterus and the findings with the curette. If, with one sweep of the curette at say six o'clock on the dial, we remove some friable necrotic material and nowhere else around the cavity is any found, then we are quite sure that in all probability a very small localized lesion exists.

Curettage should always be done, as I shall show you in a moment, in two distinct divisions, the first being curettage of the endocervix and the second curettage of the uterine cavity itself. The reason for such a distinction being made is that an adenocarcinoma of the cervix could be misinterpreted if the curette were placed in the endometrial or the uterine cavity and withdrawn. Such tissue could be delivered without recognizing that the friability of tissue didn't take place until you passed the internal os of the cervix. This would then probably be misinterpreted as a carcinoma of the endometrium, when actually it is an adenocarcinoma of the endocervix.

Figure 4 is a clinical Group III where there is extension along the endometrial cavity. Friable necrotic tissue is obtained with the curette almost the entire way around the uterine cavity. There is thickening of the wall of the uterus because of the edema, plus an irregularity and slight enlargement. As yet there has been no palpable extension beyond the uterus into the parametrial tissues.

Figure 5 shows a more proliferating mass, descending to the endocervix and at times erron-

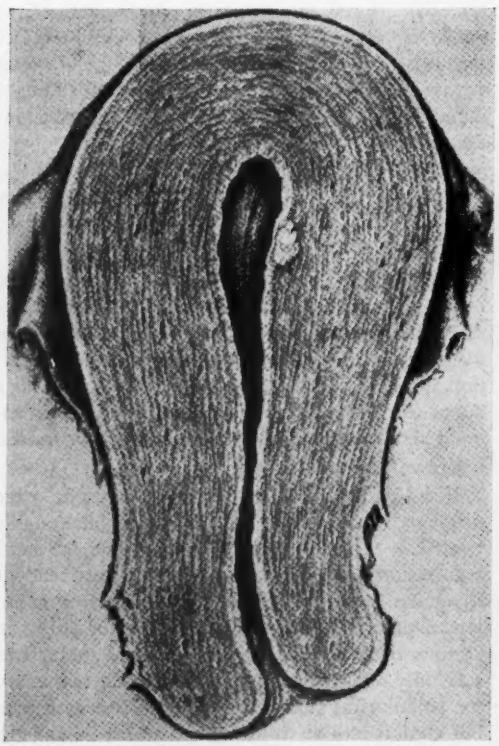

Figure 1.

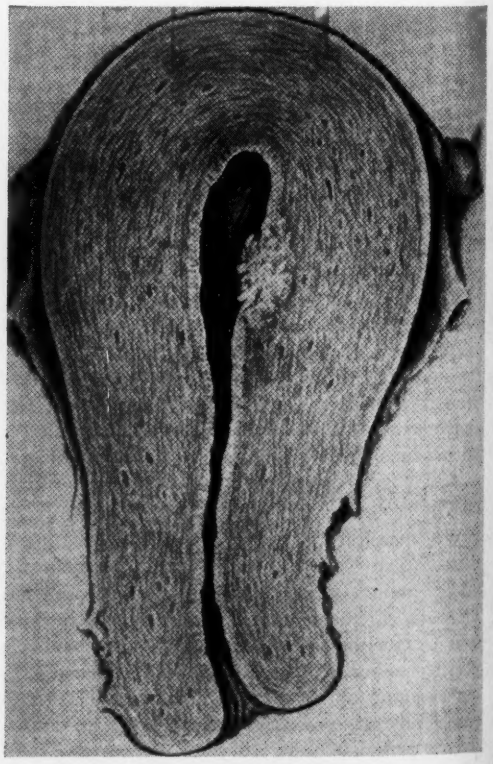

Figure 2.

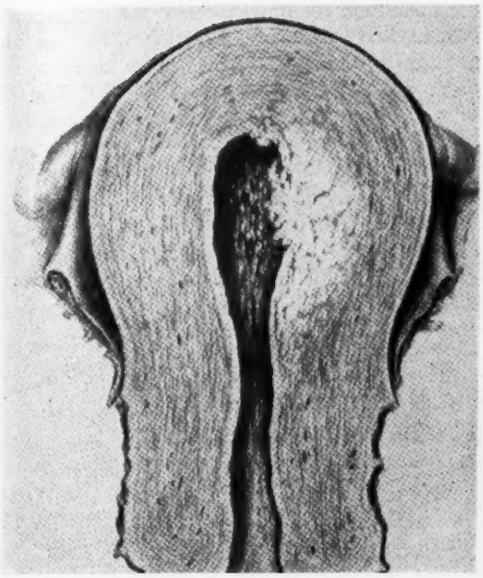

Figure 3.

eously diagnosed because of the visualization of tissue or bleeding from the cervical canal on probing, as an endocervical lesion when it is truly an endometrial lesion.

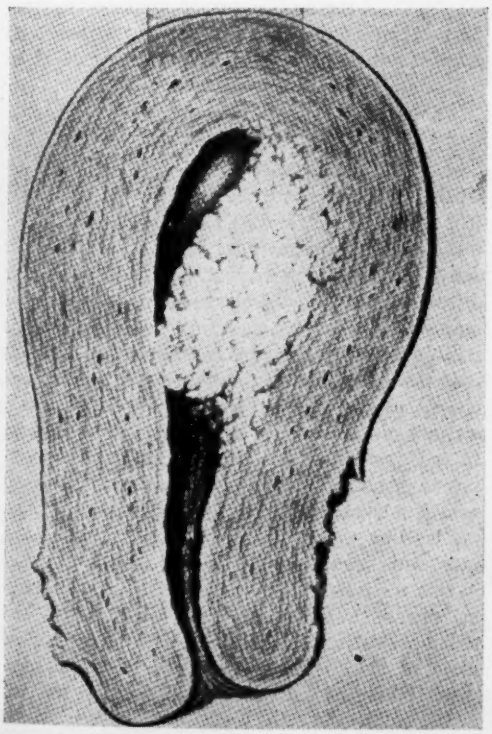

Figure 4.

Figure 6 illustrates a Group IV case where there is extension well out of the uterus. This, of course, is a far advanced carcinoma which has invaded the entire myometrium, broken through the perimetrium posteriorly and invaded the lymphatics of the pelvis and the broad ligaments. These illustrations have shown the clinical groupings of endometrial carcinoma so important for statistical studies.

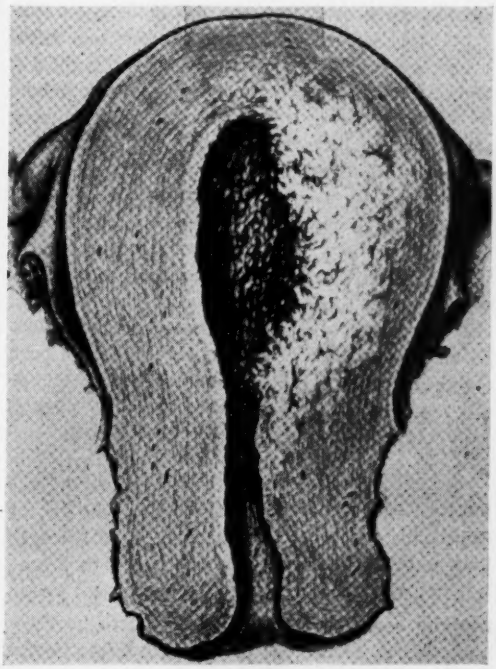

Figure 5.

All patients who present themselves for treatment are accepted in a statistical study. The curability rate in these individuals, figured on a five-year period of arrest, is extremely low. All of the previous series reported in the literature embody all of these cases. Some of them are irradiated palliatively in order to control the discharge or the bleeding or to try to relieve some of the pain and

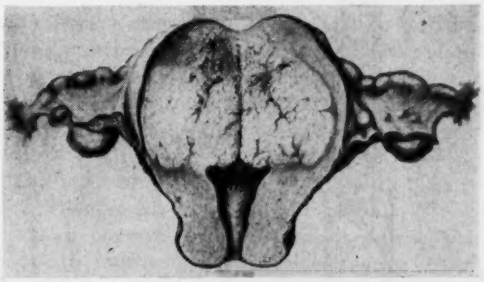

Figure 6.

the discomfort of the individual, and naturally they must be included.

If, however, we are going to exclude these far advanced cases and take the earlier group and irradiate them, we are going to be surprised in the difference of the end result.

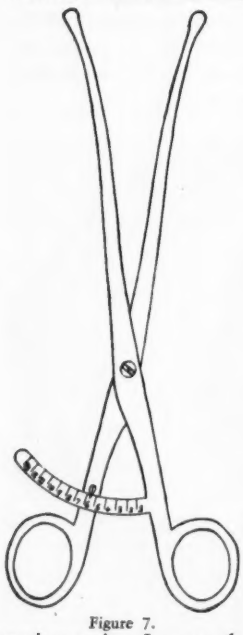

Figure 7.

All of these cases admitted into our clinic were studied in the following manner. In the first place an instrument (the uterometer, Figure 7), was used to determine the width of the cavity in the fundus of the uterus. These measurements were recorded. Then using a Y radium capsule (Figure 8) which has been reported previously, we should get a uniform and homogenous distribution of our radium irradiation within the uterine cavity. In an early lesion within the uterine cavity only the upper portion of the stem is loaded with radium. By measuring the patient very carefully we are able to figure the depth dose through the tumor and figure an accurate depth dose from our external source of irradiation. Thus we administer to these patients 6000 mgm. hours of radium within the uterine cavity and 4000 R units of x-ray within the tumor. Six to eight weeks following this procedure we remove the uterus and the adnexa so as to recover these irradiated specimens.

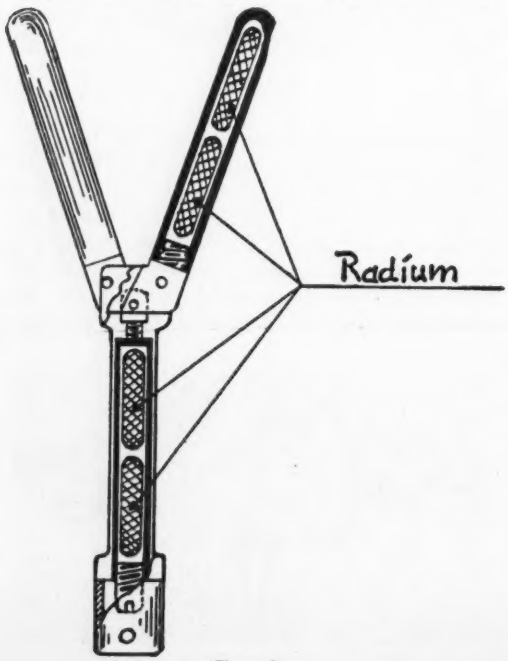

Figure 8.

In a summary of our cases it has been found that in the early superficial carcinomas of the endometrium we have been successful in destroying the carcinoma. Yet, it didn't mean to us that the treatment of endometrial carcinoma is irradiation therapy; it did mean that there is some definite effect and, therefore, it probably is of value as a preoperative measure. There have been others reporting since that time on preoperative irradiation with x-ray, and some with radium. I believe that ours is the only series that has a combination of x-ray and radium followed by surgery. The reason that I bring this out is that one is constantly questioned as to the reason for preoperative irradiation if he is going to remove the entire uterus. If you stop to think for a moment, you will immediately realize that the majority of your endometrial carcinomas succumb from distant metastases to the brain and the lung, not to direct extension within the lymphatics of the pelvis themselves. I'll grant that there are recurrences in the vault of the vagina; I'll grant that there are recurrent masses in the floor of the pelvis, but most frequently the poor end result is due to the distant metastases, which in all probability are blood stream metastases.

An interesting observation has been made that when we got into what we considered clinical Group II or clinical Group III where there was extensive infiltration into the myometrium, there was still active disease. It wasn't entrapped cellular elements, which might at a later date again undertake active mitosis and migration, but there was active disease remaining. We realized immediately that unless you had a very superficial lesion, irradiation itself, even although it be as extensive as this, was inadequate for the treatment of endometrial carcinoma. However, we were not convinced that it was not of some benefit as a preoperative measure. In order to satisfy ourselves of that, it was necessary to demonstrate some effect on the tumor which would in some way or other justify the procedure.

The first thing that we noticed in all of the uteri, after they were cut and divided into blocks so that the entire uterus could be studied for residual disease, was that the entire endometrium and the inner surface was replaced by a heavy hyaline block of tissue. The endometrium itself had completely sloughed out with probably five mm. of myometrium and was replaced by a very white glistening hyaline block of tissue throughout, with

very little change deeper in the myometrium.

The appearance of tumor tissue under the effect of the irradiation itself shows a very damaging and distinct effect. The interesting thing is the effect of this irradiation on the walls of the vessels and the vessels themselves. There is a fibrin layer folded up into the lumen completely closing it with hyaline infiltration, with edema of the intima, and the media shows throughout the so-called foam cells forming almost complete obliteration. Where is this fibrosis that we talked about following irradiation in the myometrium? It isn't there. That is a late manifestation of irradiation, not evidenced within 12 weeks to three months. So we began to realize that in all probability these changes within the walls of the vessel, the destruction of the superficial carcinoma of the endometrium, was the thing that was of value.

There should be less chance of spill with implantation into the vagina or implantation into the pelvis. There should be less chance of migration of tumor cells during the operative procedure because of the obliteration of vessels. We have carried on this work for a number of years now and have found that our over-all survival in carcinoma of the endometrium has increased to 50 per cent, including the case that comes in moribund, the case that comes in terminal, where palliative irradiation is utilized, and this group of cases. If we select those patients that had the superficial endometrial carcinoma, where there was no evidence of the disease left following the procedure of irradiation, we find that we are accumulating a group of patients with an 80 per cent five-year survival which is a distinct improvement over our previous end result.

It may be that our operative technique has improved, or it may be that we are finding more of these patients at an earlier stage of the disease. All of those things must be taken into consideration, but we still feel that with those factors being considered and being evident in other statistical studies, we eventually will display a higher survival rate because of this preoperative irradiation.

The Diagnosis And Treatment Of Cancer Of The Cervix

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In this conference on cancer we now come to another battle ground in the diagnosis and treatment of cancer—cancer of the cervix. The title of this paper limits the discussion to cancer of the cervix, but there can be no discussion of cancer of the cervix without rather general consideration of the entire female pelvis.

The Approach to the Diagnosis of Cancer

The approach to the diagnosis of cancer of the cervix must be made with a great deal of respect and with the same care and planning as that for any major operation. We must approach it with respect primarily for the difficulty in diagnosis. Too often under the pressure of a busy office or clinic insufficient time is given to the consideration of the stage and grade of involvement and the procedures necessary for the removal or destruction of the cancer.

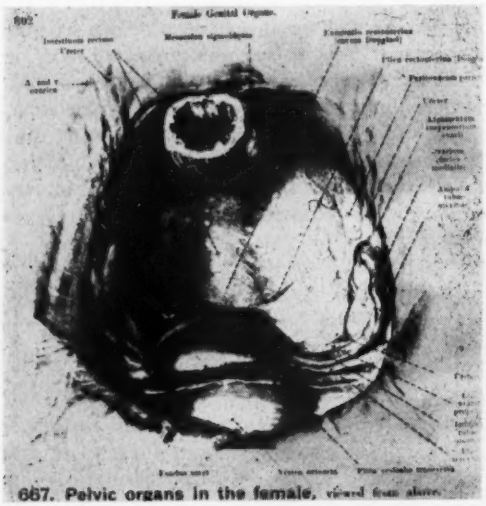
Each stage of involvement requires a different approach for the best results. No one routine technic of irradiation or surgery can be correct for all types and stages of involvement. Insufficient emphasis has been put upon this by many physicians, not excluding the author. Because cancer of the cervix is in a very strategic position to involve not only the uterus but also the floor of the bladder and rectum, and because it so often presents itself so frankly, and the diagnosis is made so easily, the surgeon or radiologist may proceed with his treatment without due consideration of the possibility of more extensive involvement than is apparent upon the first examination.

Anatomy of the Female Pelvis

Of primary importance is an intimate knowledge of the anatomy of the female pelvis, of the sites for beginning cancer, and of the method of dissemination of cancer. Looking into the pelvis from above, we find the uterus in the midline, the lymphatic chains which extend out to the ovaries, and the ovaries which as a general thing lie well out toward the perimeter of the pelvis (Figure 1). With extension from the cervix into the broad ligaments there is involvement of the ovaries and of the lymphatics.

The anatomical structures involved lie almost entirely within the birth canal (Figure 2). While the canal possesses known variations in size and shape it is, in general, a short cylinder in the center of which are the bladder, uterus, and rectum and

some intestinal viscera and the lymphatics, while near the outer walls are the ovaries and numerous lymph nodes. Surrounding this birth canal are the bony pelvis and its muscles and ligaments, and external to the bony pelvis are the structures of the thighs, buttocks, and abdomen. There is a chain of lymphatics extending outward from the uterus into the ovaries and upward along the great vessels as high as the kidneys and of course, on up into the mediastinum (Figure 3). Anyone attempting to treat or remove cancer of the cervix must give careful consideration to the extent of the involvement of the pelvis. Even in an apparently first or second



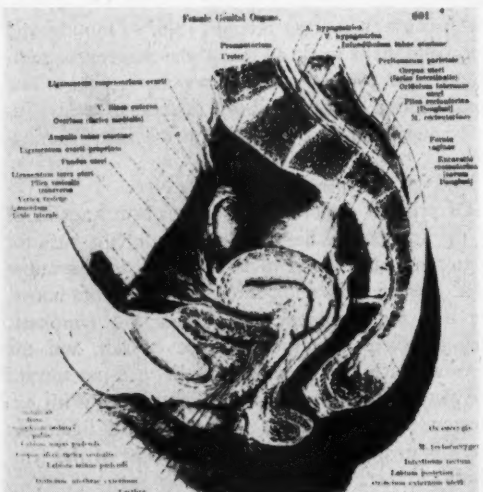


Figure 1, A and B. Anatomy of the female pelvis as viewed from above in A; and in median section in B (after Spalteholz.)

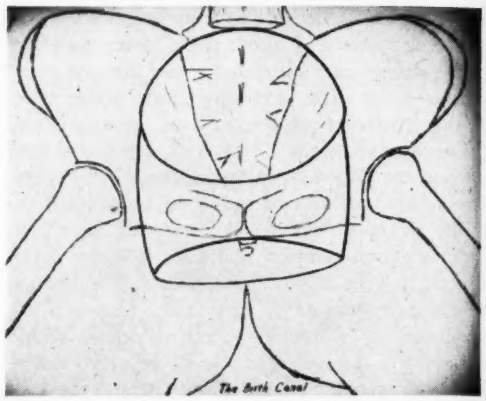


Figure 2. Birth canal which contains all the structures immediately involved from cancer of the cervix.

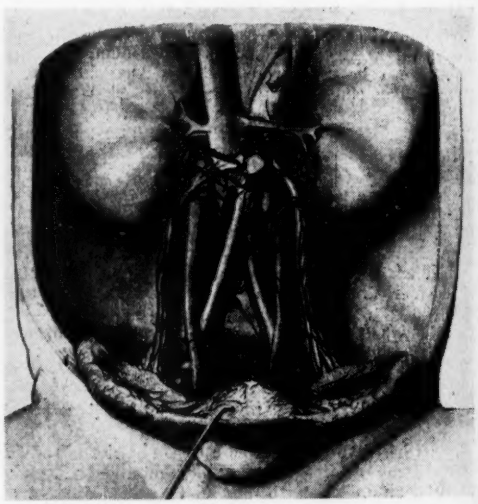


Figure 3. Lymphatic channels extending from pelvis into the upper abdomen. (After Bartels).

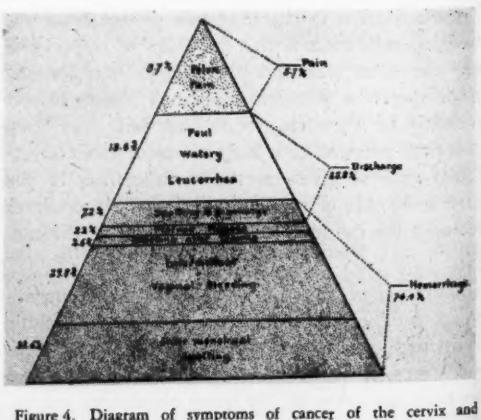


Figure 4. Diagram of symptoms of cancer of the cervix and uterus. (After Clark and Ferguson).

stage cancer of the cervix, the cancer cells may already have passed into the lymph nodes along the lateral walls of the pelvis, or as Dr. Herbert Schmitz just stated, the cells may be already lying in the lymphatics and ready to be squeezed into the lymph channels and transported to some distant part of the body, and thereby account for some of the failures of surgical operations or radiation therapy. I have had losses in treating cancer of the cervix, not because of the involvement of the uterus or the cervix itself, but because of the breaking down of a gland out along the perimeter of the pelvis, and along the bony canal. My attention had been directed too much to the involvement in the uterus and cervix. Therefore, knowledge of the female pelvis should be our first consideration.

Clinical History

The first approach to a diagnosis of cancer of the cervix is a well-taken clinical history of the patient. The age and state of health of the patient are important factors in determining the type of treatment the patient should have. Cancer of the cervix in a young girl is quite a different problem from that of cancer of the cervix in the older woman. Again, the pelvic symptoms often give clues to the extent of involvement of the cancer. Bleeding is one of the early signs but not necessarily the first evidence of cancer of the cervix. It may be associated with the menstrual period or it may be spotting between periods, or it may be a little blood that appeared after sexual intercourse. A vaginal discharge may be an even earlier symptom, or at times there is neither bleeding nor a vaginal discharge, and the cancer is found only by accident. The menstrual periods may or may not be irregular. The vaginal discharge when present is a very important sign both as to its character and its times of appearance. A watery, purulent or semipurulent discharge coming from the cervix nearly always means an extension of a cancer into the body of the uterus. Such a discharge is not common to the female. An irritation of the bladder or rectal pain may indicate extension into these organs. Pain is not a common finding: according to one author it is only present in 5.7 per cent of cases of cancer of the cervix (Figure 4). The examination of the patient must be done carefully and without undue trauma to the cervix or pelvic organs. Often the cancer cells may be lying free in the lymphatic channels ready to be displaced into the neighboring lymph nodes by undue bimanual pressure. A careful inspection of the cervix is an absolute requirement, and yet many patients have stated to me that the attending physician only did a bimanual examination.

The Examination

Sometimes cancer of the cervix is entirely silent, and it is found only by an accidental examination. As a matter of fact, every woman should have frequent examinations, and often when she is in the office for other purposes an examination of the pelvis is not a bad procedure. Beside the routine bimanual examination there are a number of laboratory and technical aids. In the examination of the cervix, many *stains* have been devised for application to the cervix, but these stains have not met with any great success. The making of a *biopsy* by taking a section of the cervix is still the method of choice, but this section may not be taken in the right location, and it may not extend high enough into the cervical canal. A modification of the biopsy method of diagnosis is the method devised by Papanicolaou which has been discussed in detail by other speakers in this conference. By this method, only a few cells are necessary for a positive diagnosis. A small curette may be safely passed into the cervical canal for the removal of tissue or cells high in the canal. Cancer of the lips of the cervix has a great tendency to progress upward along the cervical canal and is often the pitfall for either the surgeon or the radiologist. In other words, a simple inspection of the cervix with even a removal of a portion of one of the lips of the cervix is not sufficient. An examination of the cervical canal should always be made in the early stages of cancer of the cervix. A section of the lesion should be taken as they are not all malignant. Also, a curettement of the uterine cavity may be necessary in the later stages of cancer of the cervix in order to determine the extent of the malignancy. An x-ray examination of the chest for metastases is also an excellent procedure in the later stages of cancer of the cervix.

Another method for the examination of the cervix

Figure 5. Lipiodol injection of normal cervical canal and uterus.

and the uterus is the *lipiodol injection* and a roentgenogram of the cervical canal and uterine cavity (Figure 5). The lipiodol injection will often reveal an unsuspected dilatation of the cervical canal or an extension of the cancer into the uterine cavity (Figure 6). I have seen cases in which lipiodol injections were of definite help. I've even seen cases in which able gynecologists passed over with the curette a malignancy of the uterine cavity which was demonstrated by a lipiodol injection. I have disclosed small ulcers in the uterus which were no more than one cm. in diameter. On the other hand, lipiodol injections do not seem to be very popular. I am not sure as to the reason for this unless we have more confidence in the curette than we do in the lipiodol injection.

Figure 6. Lipiodol injection of cancer of the uterus.

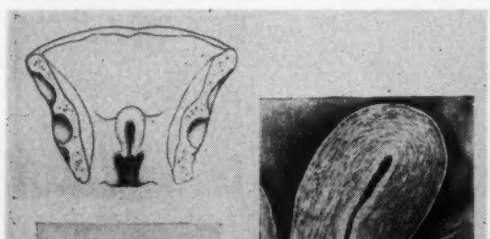


Figure 7. Cancer of the cervix, Stage I. (After Schmitz).

Discussion of the First Stage of Cancer

Now that we come to the stages of involvement of cancer of the cervix, I wish to pay respect to Dr. Henry Schmitz, the father of the preceding speaker. Dr. Henry Schmitz is responsible for the excellent basic illustrations which appeared in Surgery, Gynecology and Obstetrics in 1930, and which show the various stages of involvement. The *first stage* of cancer of the cervix, according to Dr. Schmitz, involves one lip, an area of about one cm. in diameter (Figure 7). In this type of involvement it is not satisfactory to simply look in and see an ulcerated area on the lip of the cervix. We must separate the lips of the cervix and explore as to how far this involvement may extend along the cervical canal. A small curette should be passed along the cervical canal to determine if there is still further involvement. Any tissue removed should be turned over to the pathologist for examination. If the internal os is open, that again is a bad sign. In one such case, due to the fact that I did not recognize that the simple cancer of the lip of the cervix was not limited to the lip of the cervix itself but extended along the cervical canal into the uterus, my treatment was not directed adequately to take care of this extension into the body of the uterus. Of course, the patient did not get well. In first stage cases, there must always be a gentle bimanual examination. There is no occasion for a rough examination.

When the biopsy has been taken, and the *biopsy is positive,* then the next question is: "What will be our next step?" Of course, this is all done in consultation, and consultants do have something to offer in determining the method of the removal of the cancer. Will it be surgery? Will it be radiation therapy? These are the two methods that are available for treatment.

I have no quarrel with the surgeon who wishes to remove the cervix and the uterus in this stage of involvement. It certainly has its advantages. It gives us the opportunity to examine the uterus and cervix afterward to see if we made a mistake in our approach to the case. Perhaps it is a more extensive involvement than we realized; perhaps the patient should have subsequent radiation therapy. On the other hand, I do like to have radiation therapy preceding the hysterectomy, not radium placed in the cervical canal, but intravaginal radiation therapy. Radiation treatment preceding hysterectomy offers no particular handicap to the surgeon and may overcome some of our errors in diagnosis.

Supposing that the section comes back negative. What are we going to do then? That is the problem that we must frequently face. Shall we do surgery?

Shall we have radiation therapy? Or shall we keep the patient under observation? Certainly, we are not justified in dismissing the patient and sending her home. At least, she must be kept under observation and if this ulcer, this inflammatory condition of the cervix, does not disappear, in my opinion, the patient is entitled to an operation. It may be much safer to remove the uterus and cervix surgically than subsequently to attempt to remove a cancer of the cervix with all of its attending hazards. At the time of operation, the pathologist can make a more complete study of the specimen than is possible at the time of the ordinary first examination. In these cases of inflamed cervices, if surgery is contraindicated by the condition of the patient, radiation therapy can be instituted with good results. The inflammatory conditions of the cervix and uterus do respond to radiation therapy without subsequent cancerous involvement. The observation of a patient with a dangerously inflamed cervix may require considerable time on the part of the attending physician, but the patient will be very appreciative, and a high percentage of cancer of the cervix will be avoided. The first stage of cancer of the cervix can also be cured by radiation therapy.

Discussion of the Second Stage of Cancer

The *second stage* of cancer of the cervix is that

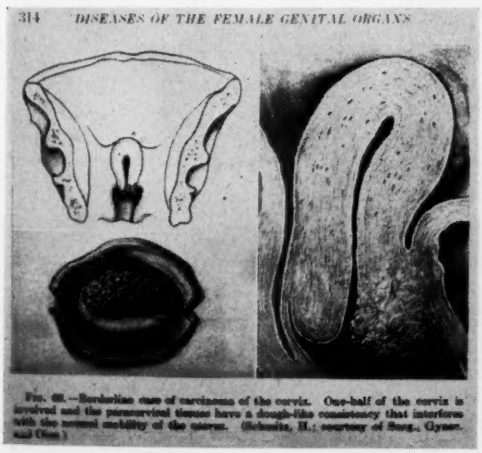


Figure 8. Cancer of the cervix, Stage II. (After Schmitz).

in which the involvement is practically the entire body of the cervix (Figure 8). In these cases there is more apt to be an extension into the lymphatic channels, and again, perhaps extending into the body of the uterus. After careful examination what shall be the next step? In my opinion, this should be radiation therapy—radiation therapy because of the likelihood of the extension into the lymphatic channels and parametrium. If radiation therapy is given, it should be adequate. It should be external radiation therapy plus intravaginal irradiation. Then the next decision we have to make is, are we going to do surgery? If we are, then perhaps radium into the cervix and uterus is unnecessary. Again, I think this is a debatable point, and I'm willing for the surgeon to operate this case after I have done adequate radiation therapy and waited for the right interval of time as Dr. Schmitz showed in cancer of the endometrium. I'm not so sure but that we may salvage a little higher percentage of our patients by so doing. If there are contraindications to surgery, then radium should be placed not only in the cervix but in the uterine cavity, because again, perhaps we are overlooking the possibility of extension into the uterine cavity. Intravaginal irradiation of the entire pelvis must be given, and that irradiation must be uniform throughout the pelvis as well as external irradiation. By such radiation therapy the second stage of cancer of the cervix can be cured.

There is also another type of cancer which is not too frequently, but occasionally, seen in which there is very little piling up of tissue at the cervix and in which there are red inflamed spots over the vaginal vault. I think of it as an inflammatory type of carcinoma. It involves the vaginal canal, and for it certainly surgery is not indicated.

Discussion of the Third Stage of Cancer

The *third stage* of involvement of cancer of the

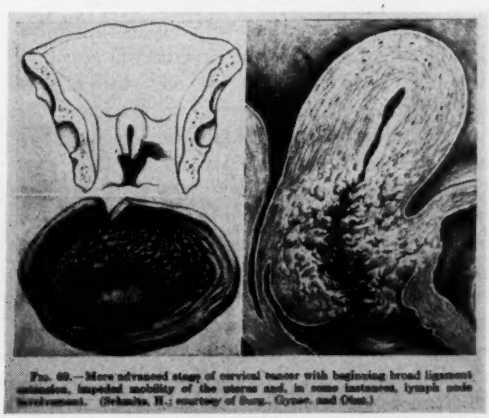


Figure 9. Cancer of the cervix, Stage III. (After Schmitz).

cervix is that in which the uterus is involved and also the parametrium (Figure 9). In my opinion, the first approach after proper diagnosis and recognition of the fact that glands in the broad ligaments are involved is that of radiation therapy—radiation therapy applied intravaginally, externally, and with radium in the cervical canal and in the uterus. The case should be followed very carefully. If there is proper response, if it looks as though by this method the patient may get well, then the

radiation therapy should be repeated. If in the judgment of the radiologist there is a possibility that this patient may not be cured, then she should be submitted to surgery. Frequently, patients come in with complete ulceration of the entire vaginal vault. Only recently, I saw two such cases. Why any woman will allow herself to get into that condition or why her

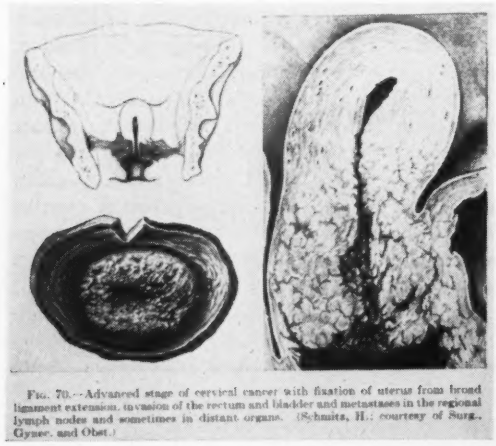


FIG. 70.--Advanced stage of cervical cancer with fixation of uterus from broad ligament extension, invasion of the rectum and bladder and metastases in the regional lymph nodes and sometimes in distant organs. (Schmitz, H.; courtesy of Surg., Gynec. and Obst.)

Figure 10. Cancer of the cervix, Stage IV. (After Schmitz).

attending physician will not recognize it, I do not know.

Discussion of the Fourth Stage of Cancer

The *fourth stage* is that with extensive involvement of practically all of the structures in the pelvis (Figure 10) and frequently with metastases to some distant portion of the body such as the lungs. For these patients, radiation therapy can offer nothing more than palliation. But 25 years ago, these same patients would lie in bed with a foul discharge soaking the bed, utterly, utterly miserable! Now at least, as the result of combined methods, such misery does not exist. Radiation therapy alone gives relief so that these patients may die reasonably comfortably; or perhaps Dr. Brunschwig will contend that surgery is able to do still more. As far as I am concerned, I can give no more than palliation, and I am delighted to have the surgeon take over such patients.

Intravaginal Radiation Therapy

One of the newer methods of radiation therapy is intravaginal radiation therapy, on which my associates and I reported in detail[1, 2, 3]. There are those who say that this method is too meticulous, too time-consuming; but I reply that if we are not willing to be industrious we should not attempt to treat cancer. Again, there are those who use the single cone method; I use the multiple cone method in order to get more complete uniform irradiation throughout the pelvis[3] (Figures 11 and 12).

The Follow-Up

The *follow-up* of the patient who has been treated for cancer of the cervix is of the greatest importance. Frequently, there is some recurrence following surgery which may be successfully treated by rad ation therapy. Also, there may be those complications of infection and necrosis of the vaginal vault from radiation therapy which require observation and treatment. The follow-up examinations should be every two weeks or more often following any one of the methods for the removal of the cancer. Only after considerable time should the interval be extended to one or two months. Examinations at six-months intervals are of no value to the patient and are only of value in compiling statistics of five-year cures. In other words, there is no substitute for industry in the treatment of cancer of the cervix.

Complications

As previously stated, one of the most common

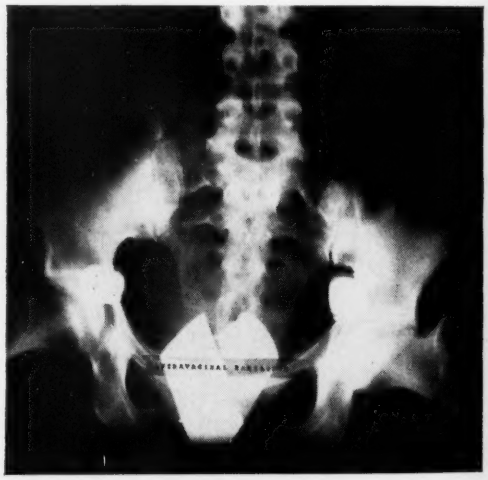


Figure 11. Roentgenogram illustrating the angles of the treatment cones which may be had in intravaginal irradiation.

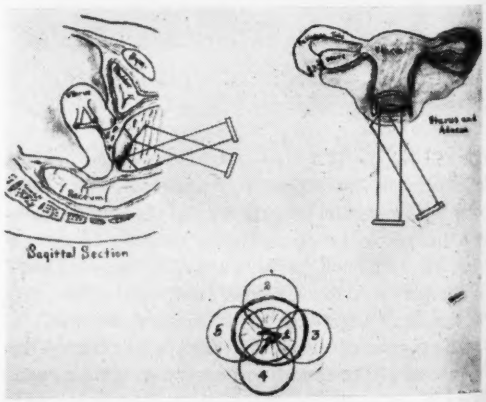


Figure 12. Diagram showing the five positions to be used in intravaginal irradiation.

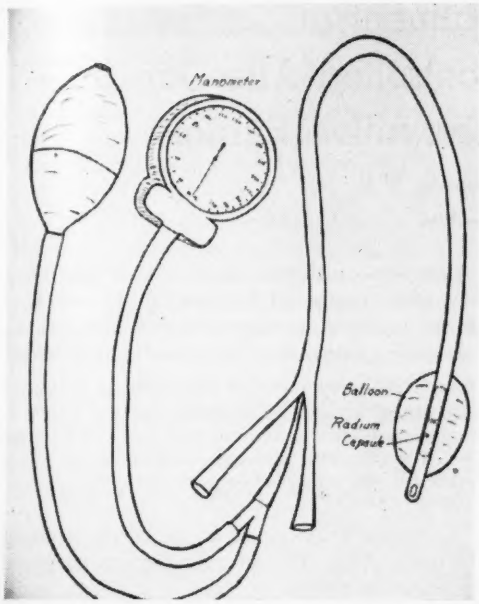


Figure 13. Retention catheter with balloon surrounding radium capsule in the catheter, and with balloon connected to manometer for use in cancer of the bladder.

complications is involvement of the floor of the bladder. With intravaginal irradiation it is possible to treat such a condition by the use of a retention catheter hooked up to a manometer (Figure 13). By using a modified bladder retention catheter, the radium may be placed inside the catheter and inserted into the urinary bladder without difficulty. The balloon surrounding the radium is then inflated to the desired extent, and this degree of inflation may be recorded and controlled by a manometer. The inflation removes the radium from contact with the tissue under treatment and at the same time gives greater depth and uniformity of dosage, which has been sought for some time in the treatment of tumors of the bladder and other cavities. I have cured at least a few cases of cancer of the floor of the bladder by this method.

The complication of rectal involvement can also be treated by the intracavity cone method and can be successful in certain types of cases. There are residual tumors following operation and recurrences after surgical operation, and both can be successfully treated by using the intravaginal irradiation and cross-firing with the external irradiation.

Failure after the use of radium in the cervix and without other radiation therapy is due to the fact that at two cm. distance from the radium there is very little irradiation. One other remark, those who are around irradiation equipment of any type should occasionally test themselves as to the amount of irradiation that they are getting. This can be done by wearing a dental film.

Conclusion

I've rather hastily gone over the anatomy of the female pelvis and some of the symptoms of cancer of the cervix. I have tried to outline the method of attack at the different stages of cancer of the cervix. I wish to say that while I'm not quoting statistics, yet I do not have the fear of the first and second stages of cancer of the cervix that I used to have, and I have seen some very excellent results even in the third stage. I have seen cures of residual tumors following operation.

The procedures which I have offered for the treatment and management of cancer of the cervix are my present way of thinking after many years of successes and failures. I reserve the right to change my opinion as our knowledge of the subject warrants.

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The Radical Surgical Treatment of Cancer of the Cervix, Recurrent and Uncontrolled After Previous Irradiation and Conservative Surgery

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The management of cancer of the uterus depends upon whether the lesion is in the cervix or primary in the corpus. The standard treatment for cancer of the cervix at present is irradiation by means of radium applied locally and roentgen rays administered in the form of pelvic cycles. Persistence of neoplasm, or its recurrence at a later date, usually is treated by additional applications of radium and roentgen rays. When these secondary courses of treatments are of necessity carried out, the prognosis is very grave indeed.

It is a fact, however, that recurrent or persistent cervical cancer may be still localized to the site of origin or at least to the pelvis. Cancer of the cervix remains in the pelvis for relatively long periods before metastasizing widely. Death in at least half of these patients is the result of uremia due to constriction of the ureters, hemorrhage due to erosion into large pelvic vessels, or infection due to septicemia arising from the large necrotic masses in the pelvis.

In recent months, at the Memorial Hospital, we have initiated a surgical program to attempt a salvage of patients with cancer of the cervix, persistent or recurrent, after radiation therapy and who also may have had conservative surgical procedures. These patients may be grouped for purposes of discussion as follows:

1. Recurrent or persistent cervical carcinoma limited to the cervix and immediately adjacent areas. Although not generally practiced, the fact that the growths are anatomically limited to the cervical region permits of a wide resection (radical panhysterectomy with pelvic lymph node dissection).

(Lantern slides were shown of several surgical specimens.)

Total number of patients submitted to operation	23
Surgical mortality	0
Number of patients in whom slough and induration were present without tumor (living and well six months and one year respectively)	2
Recurrences present or since died of disease	5
Living and well without evidence of recurrence three months to one year	11
Excision of uterus for palliation but disease left behind	5

2. Recurrent carcinoma of cervix that has involved the bladder.

Complete excision necessitates total cystectomy, total hysterectomy and vaginectomy. This has been carried out as a one-stage procedure and entails a bilateral implantation of the ureters into the colon.

(Lantern slides were shown of several surgical specimens.)

Total number of patients submitted to operation	17
Surgical mortality	6 (35%)
Died of recurrences or persistent disease	5
Living and well without evidence of recurrence up to 13 months	6

3. Recurrent carcinoma of the cervix involving the pelvic colon. This situation requires no special comment since there has been no hesitancy in the past in performing total hysterectomy and vaginectomy in conjunction with combined abdomino perineal resection for carcinoma of the rectal colon extending forward. In the case of carcinoma of the cervix extending into the rectum, the same procedure is carried out.

4. Recurrent carcinoma of the cervix involving both rectum and bladder.

A very radical one-stage procedure has been devised for excision of all pelvic viscera. This requires an end-to-end colostomy with ureters implanted into the upper sigmoid above the colostomy. The steps in the procedure are as follows:

Anesthesia: Continuous spinal or intratracheal ether has been used.

At the beginning of the operation saline and then blood are administered intravenously.

Abdominal Phase

1. The low midline incision extends a few centimeters above the umbilicus. The abdomen is palpated and inspected to confirm the absence of metastases.

2. The patient is placed in the Trendelenburg position and the bowels packed upward with laparotomy pads. The posterior parietal peritoneum over the bifurcation of the aorta is incised, these incisions being carried downward over the right external iliac artery. The right ovarian vessels and ligament are ligated and divided. The lymph nodes, and periarterial and perivenous tissue are dissected downward on the right side. The right hypogastric artery and vein near the bifurcation of the common iliac is isolated, ligated, and transected.

3. The mesosigmoid is divided over the left

common iliac vessels and the sigmoid colon pushed upward. The left ovarian suspensory ligament and vessels are ligated and divided. The lymph nodes and perivascular tissues of the left common iliac and external iliac vessels are dissected downward. The left hypogastric artery and vein near the bifurcation of the left common iliac vessel are isolated, ligated, and divided.

4. On the right side, the round ligament of the uterus is divided near the abdominal wall. The contents of the right obturator fossa and right side of the pelvis are so dissected as to mobilize these tissues en bloc mesially. The obturator vein is divided but the obturator nerve is preserved and pushed laterally to lie freely near the right pelvic wall. The arteries and veins coursing from the right pelvic wall to the tissue that has been retracted mesially are ligated and divided.

5. The peritoneal reflection from the anterior abdominal wall onto the bladder is divided, and the latter separated from the symphysis pubis. The bladder is completely mobilized except for its attachments at the base.

6. The areolar tissues on the left side of the pelvis and in the left obturator fossa are completely dissected and mobilized mesially as described under "4" for the right side.

7. Both ureters are divided at a convenient level, well above any gross evidence of involvement by neoplasm. In mobilizing the ureters, care is exercised not to remove too much periureteral tissue. This tends to prevent necrosis of the ureters.

8. First one and then the other of the ureters is implanted into the sigmoid colon. The sites of implantation vary depending upon the redundancy of the sigmoid and the length of the ureters remaining. Needless to add, the implantations are made in such a manner as to avoid sharp angulations. In three instances in the series herein reported, the right ureter was implanted into the cecum. The ureteral implantations are carried out essentially according to the Coffey-I method.

9. The upper pelvic colon is transected and each cut end invaginated by a purse-string suture. The mesopelvic colon is divided with preservation of the blood supply to the sigmoid.

10. The pelvic colon is dissected away from the concavity of sacrum and mobilized completely down to the pelvic floor.

11. At this stage, all the pelvic viscera are isolated and mobilized except for the attachments to the pelvic floor. The abdominal wound is closed, with the end of the sigmoid brought out through the midline incision. When the wound is closed the colostomy is opened. A hard rubber tube drain extending into the pelvis is inserted in the lower angle of the wound.

Perineal Phase

12. The patient is placed in the lithotomy position. The vaginal introitus is closed by continuous suture and the anus by a purse-string suture.

13. Elliptical incisions are made to encompass introitus and anus and extend from the tip of the coccyx to below the clitoris which is preserved. The dissection is carried upward and the levator ani muscles are divided.

14. The pelvic contents, en masse, are taken out of the pelvis from below.

15. The perineal wound is closed. The deeper soft tissues are approximated and the skin is closed with interrupted chromic catgut sutures. Usually there is blood exuding from the large raw surfaces of the pelvic walls, so gauze packs are placed against the hollow of the sacrum. These are brought out through the posterior angle of the wound. A rubber tube drain is brought out through the anterior angle of the wound just below the clitoris.

Up to the present, 44 patients have been subjected to this procedure.

(Lantern slides were shown of several surgical specimens and patients.)

Number of patients operated upon	44
Surgical deaths	11 (25%)
Since died of disease	12 (27%)
Living with metastases	3 (7%)
Recently operated	2
Living and well without evidence of metastases	16 (36%)
Living and well for one year	4

If the entire series of patients is considered as unequivocally lost because of the presence of recurrent or persistent disease after failure of standard therapeutic measures the following summary may be presented.

Total number of cases	84
Surgical deaths	17 (20%)
Second recurrence present or dead of disease after secondary operation	25 (30%)
Living, well without evidence of active disease (Few months to over one year)	33 (39%)

The interesting fact is that 33 or 39 per cent of the series at this writing have been rendered free from evidences of active neoplastic disease for periods varying from several months to over a year.

Of course, it is to be anticipated that the large majority or all these survivors will eventually succumb but an appreciable palliation has been afforded and if experiences with other forms of advanced abdominal cancer can mean anything, some of these patients might be permitted to survive for prolonged periods. Only further and more prolonged experience with this type of surgery can provide more definite information along these lines.

Malignant Melanoma of the Skin

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Any pathologist who looks at any number of so-called nevi and malignant melanomas will develop a certain amount of humility, for the chances of error are always present. In discussing the malignant melanomas of the skin, I do not wish to include malignant melanomas occurring in other locations. In our experience perhaps one out of every 40 cases of skin cancer turns out to be a malignant melanoma of the skin. You cannot speak of malignant melanomas of the skin without speaking of nevi. The word nevus by definition means mark, and probably it would be more proper to call them moles. Everyone has moles, but only a small percentage undergoes malignant change. It is very infrequent for the verrucoid type of mole to become malignant, and the hairy mole only rarely becomes malignant. Usually it is stated that the black mole most frequently undergoes such transformation. I think it is probable in quite a number of instances that a black mole is already a malignant melanoma when it is first seen. It was my impression, after going over 75 cases of malignant melanoma, that one of the most frequent types of moles which is going to undergo transformation is the flat, soft, mole which is hairless and only very slightly elevated (Ackerman, Bloch).

In a survey of this group of 75 cases I tried my best to find out whether any pre-existing mole was present.

Location of Lesions

Location of Lesions	*Number*	*Per Cent*	*Previous Mole*
Lower extremities	26	35	21
Head and neck	24	32	10
Chest	16	21	10
Upper extremities	7	9	4
Trunk	2	3	1

This series demonstrated that malignant melanoma is most common in the head and neck area and the lower extremities, with a fair number on the chest. In about 65 per cent of instances through the history and examination of the specimen a mole was present that in time became a melanocarcinoma, although you must remember that only a small fraction of all moles ever does undergo such transition (Webster). In a high percentage of instances the mole had been present since childhood.

Can you by the microscopic examination tell what kind of mole is more apt to become a malignant melanoma? The mole is a congenital malformation and, unlike other processes, although benign, it has no boundaries. It can show different microscopic patterns. These neval cells can be mainly within the dermis, rarely entirely within the epidermis, or they can be what has been termed junction nevi in which neval cells will be both in the dermis and seemingly within the epidermis. There is some evidence that the melanocarcinomas arise more frequently in junction type moles (Becker, Allen). In this group, and in all moles (with rare exceptions) that I was able to find in a survey of several of the large hospitals in St. Louis, all those below the knee were junction type. It is certainly true that only infrequently will an intradermal nevus become a malignant melanoma.

There are certain microscopic changes which enable the pathologist to tell when a mole has become malignant. The earliest changes first occur in groups of cells. These malignant cells show enlargement not only in the cytoplasm but in the nucleus. In the nucleus there may be very prominent nucleoli, and mitotic figures can appear. You may even see nests of tumor cells deep within the lymphatics.

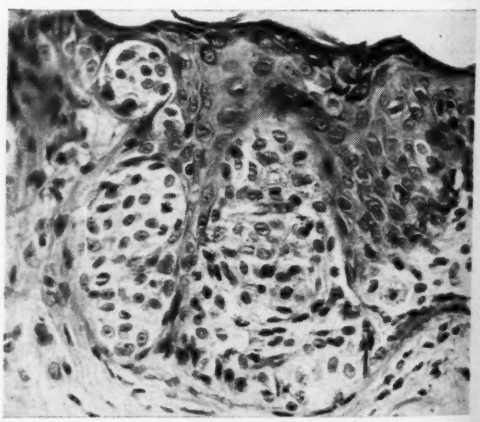


Figure 1—Photograph of an early melanocarcinoma in an adult. Note large cells with prominent cytoplasms, prominent nuclei and nucleoli. There are also several mitotic figures present.

What are the clinical changes in a mole which should excite suspicion? The danger signs are *increase in size, deepening of pigmentation* and *ulceration.* There are certain indications for mole removal. Any mole located in an area subjected to chronic irritation, around the collar, the belt, or the region of the shoe, should be removed. Any mole which is undergoing increase in size, deepening of

pigmentation should probably be removed. It is also probably justified to remove moles below the knee which are flat, soft, brown and hairless.

The clinical pattern of malignant melanoma can vary remarkably. In most instances, especially when it is deeply pigmented, you can diagnose the case simply by looking at the patient. If you have a tumor (not a wart) on the plantar surface of the foot, you must consider it to be a malignant melanoma until proven otherwise. In fact, the most common malignant tumor of the lower extremities is the malignant melanoma. I have probably seen more

Figure 2—Ulcerating relatively nonpigmented melanoma of the plantar surface of the foot.

of these tumors treated incorrectly on or around the plantar surface of the foot than in any other area. They are often incised as abscesses, curetted, or inadequately removed.

If a pigmented tumor appears in the subungual area it is often thought of as an infection, but it is usually a malignant melanoma. Other tumors, such as the glomus tumor, have an entirely different clinical pattern with usually exquisite pain. Rarely a malignant melanoma can grow superficially and this

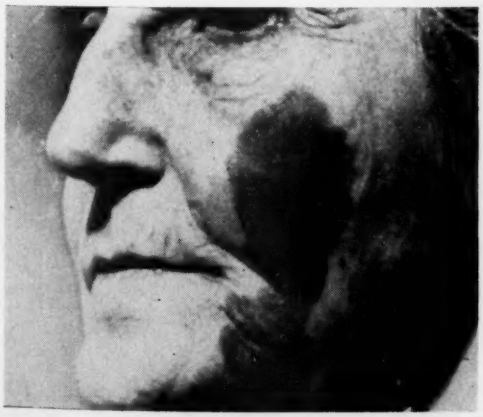


Figure 3—Freckle type of malignant melanoma growing superficially and of 10 years duration.

is designated as the freckle type of malignant melanoma. They grow slowly and may remain localized for many years. They are very reluctant to metastasize to regional nodes. At this point I might say something about biopsying a malignant melanoma. We have not been able to obtain evidence than an incisional biopsy of a questionable pigmented tumor, even if it proves to be a malignant melanoma, has ever caused any harm. In some instances biopsy may be necessary, particularly when the tumor is growing in an area where a radical excision would imply deformity or considerable plastic repair. If such a neoplasm is in an area where excision will not imply such unfavorable factors, then the surgeon can at once proceed to radically excise the lesion.

How do you recognize melanocarcinoma when you see it under the microscope? One of its most characteristic qualities is its production of melanin pigment. Now melanin pigment is usually confused with hemosiderin. Let us say that we have a tumor which is suspected of being melanocarcinoma and that there is pigment in it and we wish to prove that pigment is melanin pigment. In the first place, practically all malignant melanomas have pigment to some extent within the tumor. This pigment may be very small in amount, and you may need a great

Figure 4—Clinical example of fungating deeply pigmented malignant melanoma.

many sections. At times silver stains (Fontana) may bring out hidden melanin. Sometimes superficial biopsies will show no pigment and the deeper areas will show large amounts of pigment. An iron stain stains the hemosiderin a brilliant blue and the melanin pigment retains its brown dull appearance. Hemosiderin is golden yellow, coarse and refractile, while the melanin pigment is fine, brown, and nonrefractile.

Unfortunately, the presence of melanin pigment within a tumor does not necessarily mean that that

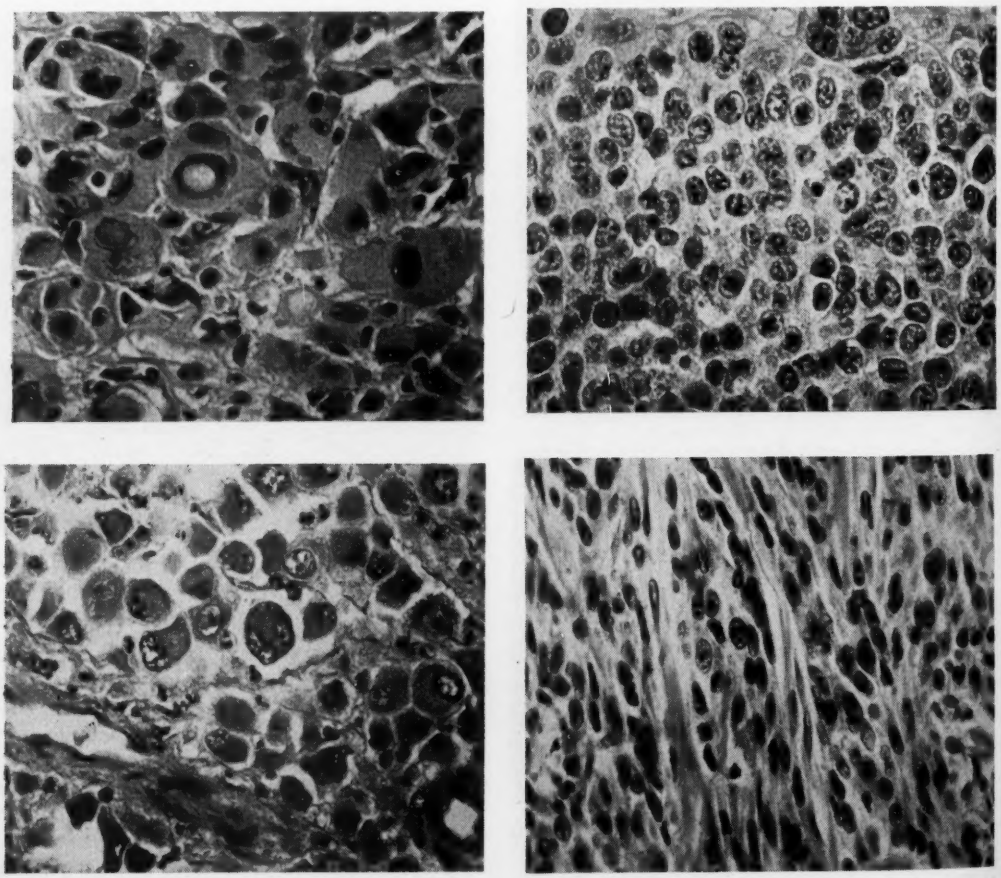
person has a melanocarcinoma. A basal cell carcinoma may be pigmented by melanin pigment and confused clinically with a malignant melanoma. This can be distinguished microscopically, for it has the characteristic pattern of a basal cell carcinoma. Epidermoid carcinomas rarely may also contain melanin pigment (Khanolkar, Stewart). Pigmented benign lesions of the skin may contain melanin pigment and thus also be confusing.

At times a reticulin stain may be helpful for it may reveal rather characteristic patterns, but this pattern is certainly not absolute. Also, you may find small nests of cells in malignant melanomas which are very similar to the nests of cells which one sees in a perfectly benign mole.

In the relatively non-pigmented melanoma the microscopic pattern may vary in an individual tumor. It may also vary in the primary and the metastases. It may superficially resemble an epidermoid carcinoma, a fibrosarcoma, a lymphosarcoma or a ganglioneuroma.

This rapidly growing tumor with its tendency to spread rapidly by both the blood stream and the lymphatics can go to practically any organ and grow there. Its growth pattern within lymph nodes has some practical significance, for when this tumor metastasizes to a lymph node, it replaces the node with very little reaction. We have found that when the regional nodes draining a malignant melanoma are enlarged, this enlargement indicates that the patient has metastases to these nodes unless there is prominent infection in the primary. Occult clinical metastases may be impossible to palpate and this will be particularly true in the axillary area.

How should you treat these malignant melanomas? There is no evidence that hormone therapy or castration has been of value. In practically all instances this tumor is exceedingly refractory to irradiation, which may be related to its neuroectodermal origin. Probably many instances of malignant melanomas reported in the literature as cured by irradiation were either not confirmed microscopically or were mis-



Figures 5-8—Bewildering variation of microscopic pattern in four Proven cases of malignant melanoma of the skin.

diagnosed by the pathologist. Perhaps they were pigmented tumors but were not in the malignant melanoma group.

We feel that the treatment of a malignant melanoma is radical surgical excision combined with radical dissection of the lymph node draining area when such areas are predictable. If a tumor is on the leg, you are going to dissect the inguinal node area, or if it is on the head or neck you are going to dissect the neck nodes. However, if the tumor is growing in the mid-abdomen, then the lymph node drainage area is not predictable.

The prognosis is difficult to evaluate in a single case. You can make certain general statements about prognosis. In the pre-pubertal child a malignant melanoma has a very strong probability that it will behave in a fairly benign fashion for there are only rare instances of metastases in this group (Spitz).

The sex, presence or absence of melanin and the microscopic pattern have no effect on prognosis. The amount of reticulin in the tumor, the amount of the pigment in the tumor or the metastases do not seem to bear any relation to the prognosis. The freckle type of tumor (a superficial lesion) has a much better prognosis because of its reluctance to metastasize. The subungual type, of course, also grows rather slowly and is best treated by amputation of the finger and axillary node dissection. The location in the head and neck area has a favorable outlook. Probably there are two explanations: in the first place, these patients will go to a physician more quickly than if they had something growing on their lower extremities. In our series the time interval in the head and neck area before the patient visited a physician was just half that of the foot. Secondly, lymph node dissections of the cervical lymph nodes are much better surgical procedures and much more complete than dissection of the inguinal area. No previous treatment is of very great importance. However, I didn't have any evidence that previous bad treatment speeds up the process; the average length of life in those who died either with or without treatment was about the same. Now, certainly those patients who have primary radical surgical excision with regional node dissection are going to have a much better outlook than the group with poorly conceived excisions and no regional node dissections.

Perhaps I should also say something about the dissection in continuity (Pack). The malignant melanoma is a very rapidly growing neoplasm and it metastasizes readily. If the tumor is located fairly close to the lymph node bearing group to which it drains then it will be logical and quite simple to do a dissection in continuity. For instance, if a tumor is located on the leg very close to the groin, dissection in continuity would be logical. In a similar fashion, if it is located on the face, then dissection in continuity could be done. But if the tumor is located on the big toe and you have questionable node involvement of the inguinal region, I am not in favor of dissection in continuity. Neither am I in favor of hemipelvectomy or interscapulo-thoracic amputation. If the tumor is located on the lower extremities, the trunk or the abdomen, the prognosis is probably much poorer because of the unpredictability of the lymph node drainage. If the nodes are involved but not fixed, then it is quite unfavorable, but there should be no hesitation in operating a patient with involved nodes. Certainly the greater number of the nodes involved the worse the prognosis, and if the patient has satellite skin nodules the prognosis is usually hopeless.

If the patient has persistent melanuria we have found that the prognosis is hopeless. If the nodes are fixed or if distant metastases are present the prognosis is hopeless.

In primarily treated cases of malignant melanoma in which regional node dissection is done and when those areas are predictable, it is possible to get a very satisfactory five-year survival. I believe that when this tumor is found it should be treated without delay by radical excision and radical node dissection when such areas are predictable.

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Benign Lesions Of The Breast

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Cancer of the breast remains one of the most common of all cancers. In spite of our efforts to be optimistic about the disease, the end results in many instances are such that it is easy to lead to a feeling of intense pessimism. This has been true particularly in the psychic makeup of most women with lesions of the breast. There is hardly a woman who has not had a neighbor or a friend who has died from cancer of the breast. These deaths often have been most miserable. At the same time there is hardly a woman who has not had a friend operated upon for cancer of the breast with survival. This latter woman, however, never tells about her cure. It is kept a deep secret. As a rule, when the average individual discovers a lesion in her breast, she does one of two things. She becomes terrified and afraid to find out the true nature of the lesion, and does not seek medical advice until late; or she becomes frightened at the slightest disability and confronts her physician often with insignificant disturbances.

This latter situation produces a very interesting psychologic situation. The apprehension on the part of the patient is a very contagious thing. Her husband immediately has the same feeling, and this attitude can be very easily conveyed to the examining physician. This physician may react in one of several ways. He may tell the patient that the lesion is of no significance and to pay but little attention to it. Again, in his apprehension, he may be unusually radical in taking care of a lesion that is completely benign. Obviously, the logical course should be for the physician to understand the exact nature of the lesion, for then the proper care becomes much easier to carry out.

It has been my experience when we are confronted with a patient who has a lesion in her breast, there are two fundamental questions in her mind which, as a rule, she never asks. She first wants to know if the lesion is malignant. If she can be promised that it is benign, the next question is, "What is its natural history? Will it ever develop into cancer." We, therefore, must be in a position to answer both of these questions definitely in giving our patient advice. Fortunately, we always can find the answer of the former question. The lesion can always be removed and examined microscopically and the diagnosis of cancer confirmed or the disease proved not to exist. It is in the so-called benign lesion that many physicians get into difficulty. Often he cannot distinguish between the two on physical examination. However, the more adept the clinician becomes the less he has to rely on biopsy. At the same time there is no excuse ever for a physician to allow a mass to exist in the breast, the nature of which he does not know, until the passage of time determines the true nature of the disease. This is one of the most dangerous of the differential methods of which we know in determining whether a lesion of the breast is benign or malignant. We, therefore, must begin with the attitude that when a patient confronts us with a lesion in the breast we must decide then and there whether or not the lesion is malignant. If the lesion is not malignant, biopsy often gives us considerable information as to the subsequent course of events. Therefore, the benign lesion becomes most important to us; and it is this phase of the breast problem which I should like to discuss this afternoon.

My thesis will be a simple one. It is dependent upon the fact that the development and the basic structure of the breast are dependent upon the action of certain hormones acting upon breast tissue and that structural malformations in the breast of a benign sort are a result of a disparagement in the relative reaction of these hormones in the breast as related to normal secretion and normal structure. Thus, the entire story of benign lesions of the breast will represent not a group of different diseases but a continuum, dependent upon the reaction over a long period of time of certain structures to certain stimuli. One might consider then the pathology of the breast as a type of pathology in the fourth dimension because it is affected by time. The lesion which a girl will show in the late teens or the early twenties may change completely in the thirties and even more in the later thirties. The breast then is not a static viscus. It is extremely dynamic in its structure, and your patient will have a different picture at different periods of her life.

In order to substantiate this thesis, I want to consider certain abnormalities in the breast as related to sex hormonal secretions. In the beginning before puberty the male and female breasts are identical. They exist as a small group of major ducts directly beneath the nipple. As puberty begins, at first the breast is affected by the secretion of estrogen. The effect of this hormone on breast structure is variable. By and large, it produces an increase in the length of the duct, an increase in the diameter of the duct, and epithelial growth. It also has to do with water retention and tends to produce normally a faint edema of surrounding fibrous tissue of the duct.

There is another secretion from the ovary which comes along a little bit later in life when ovulation begins. That is the secretion from the corpus luteum. This, as is well known, is called progesterone. The action of progesterone is to form alveoli. It changes the terminal duct from one with an ending that looks like a test tube to an ending that looks like a bunch of grapes. In some animals, the macaque monkey, for instance, estrogen will to a certain extent form acini. It is probable in some humans that estrogens also form some of the alveoli. By and large, however, alveolar formation is a function of progesterone. Progesterone tends to act as a physiologic antagonist to the estrogen. While it is producing the alveoli or the acini, it also tends to decrease the extent of duct formation as well as periductal edema. Therefore, in a way two stimuli from the ovary also may be physiological antagonists.

I think we would make a mistake were we to think that all breast tissue is affected equally and simultaneously by either of these two secretory agents. It will be realized that the breast requires several years for its formation during the period of puberty. Another example of the time effect on breast structure is seen in the growth of the breast during pregnancy. Although the corpus luteum of pregnancy is constantly secreting, it is not until about four and one-half or five months that complete acinar development exists. Many of the acini are formed within the first two or three weeks but others not for a very long time. During active sexual life, therefore, many of the cellular structures of the breast do not respond to hormone action identically. Again, all women do not ovulate at the same chronological time month after month. This is a familiar observation. Furthermore, women will continue to have estrogen secretion long after ovulation has ceased. Menstruation is a common phenomenon in the later forties but pregnancy is not. That the lack of ovulation and, thus, corpus luteum formation might play a part in forming an imbalance in ovarian hormonal secretion, is suggested by a review of some of our patients a few years ago at the Barnes Hospital in Saint Louis. We felt that if there were a relative estrogen hypersecretion it might be explained by the infrequency of ovulation. We, therefore, studied the frequency of pregnancy in women with benign lesions of the breast as compared to the statistical occurrence in women of this region. It is interesting to note that pregnancy was approximately one-half as common in women who have benign lesions of the breast as in normal individuals of that age period. In all probability, there will be a dislocation at times in the relationship between the secretion of estrogen and the secretion of progesterone by the ovary. Again, there is a complicating situation in the effect of the adrenal cortex. We know very little about its action on breast structure in normal situations. We do know that it can affect these breast structures.

Usually the first pathologic situation encountered in the breast is seen in boys at about the age of 14 to 18 years; that is, during puberty. It is due to the fact that the testis also is a great source of estrogen secretion, perhaps as great as the ovary. Normally this estrogen secretion on the part of the testis is counterbalanced by androsterone secretion on the part of the interstitial cells. There are times, however, in the adjustments of increased secretions during puberty in which the amount of estrogen produced by the testis outweighs the amount of testosterone which ordinarily would counteract it physiologically. This results in a small button-like enlargement under one or both nipples. This enlargement usually is very tender and very embarrassing. If that tissue is removed, one can see that there is epithelial hyperplasia, periductal edema, and budding on the ducts. It resembles the picture that one sees experimentally in the human male with the injection of large amounts of estrogen. This lesion never does harm. It is not a precancerous lesion. It really is not gynecomastia. It is a hormonal mastitis in the sense that there are inflammatory cells and it is tender. The physician can promise his patient, if the lesion is left alone everything will soon be all right. One can hasten this process by giving male sex hormone in the form of methyltestosterone. Certainly there is no excuse for excising the nipple in the treatment of the disease unless it is done purely for tenderness.

One can have gynecomastia, however, that is of a much more massive type. Such a type may be due to, or may be associated with, primary tumors of the testis. It also may be associated with a primary tumor of the adrenal cortex. Interestingly enough, however, tumors of the adrenal cortex in young boys produce feminization and in girls masculinization. At the same time one must be careful to explore the possibility of such adrenal or testicular lesions before considering true gynecomastia a simple hormonal imbalance which, in all probability, will readjust itself.

The microscopic picture in massive gynecomastia is characteristic. There is an enormous amount of edema, clear-staining cells, and a considerable amount of budding. The inflammatory process has disappeared. It is a much more difficult problem to produce involution in this type of gynecomastia than in the other preceding type of mastitis. In most instances in my experience, however, it has been benefited markedly by the use of the male sex hormone.

In the female one of the earliest changes, besides

the beginning development of the form of the breast which comes as a result of the duct system and lobule system, is the appearance of pigmentation around the areola and what seems to be small elevated nodules around this pigmented area. These modified sebaceous glands, or the glands of Montgomery, are formed by the action of sex hormones. They will get larger during menstrual time and larger during pregnancy. Their function obviously is one of lubrication to prevent cracking of the areola and cracking of the nipple. They are of no significance clinically except occasionally as a result of trauma this lipid material will be extruded into the surrounding tissue and a foreign body granulomatous process set up. It mimics tuberculosis microscopically and it mimics syphilis microscopically. Excision is the treatment of choice, and one has only to excise the skin of the areola which is involved and not carry the exicision down into the duct system.

We recently have been able to study the breast of a patient with a tumor of the adrenal cortex that produced masculinization at about the age of 30. Up until then she apparently had been normal. She developed a beard, her voice became coarse, her breasts became flabby, and on microscopic section there was no periductal edema. In fact, one saw but few ducts and these were small. The outstanding appearance was the residue of the acinar system. The ductal system had become atrophic. While this apparently was not progesterone that was secreted by the adrenal cortex, it was one of the 17 ketosteroids that chemically was closely related to progesterone. The observation tends to substantiate the apparent antagonism between the progesteronal group of hormones and the estrogen group.

I think it is important that we remember this picture, because then it gives us an opportunity to understand what will happen to the female breast when we give large doses of the male hormone.

In the female one of the earliest manifestations of morphologic alteration that is the result of an abnormal response to chemical stimulus is the so-called fibroadenoma. This is a small area of breast tissue, which for some strange reason has reacted differently to the estrogens than has the rest of the breast. The ducts are dividing profusely. There is a tremendous amount of edema. Where such edema is extensive, the term adenomyxoma often is used. Such edema is due to retention of fluid very much as one sees in the endometrium, probably as the result of a female sex hormone. This naturally creates a need for more space, and as it does it presses into the normal breast tissue and forms an adventitious capsule. It is within the breast tissue so that it can be moved around as one would a small hickory nut. The adenofibroma, then, probably is not a true tumor.

When an adenofibroma occurs in the early twenties, one sees less edema. More commonly there are multiple encapsulations with beginning dilatation of the ducts. Intracanalicular development is common. In the later twenties, thick collagen begins to appear in the stroma. The ducts become tremendous and fibroblastic proliferation, which probably is secondary to the edema, enfolds into the ducts, giving the striking appearance of intracanalicular fibroadenoma.

The gross appearance of the lesion is obvious from its microscopic structure. The expanding focal growth has formed a capsule under a great deal of tension. It has been a slow expanding lesion and, therefore, when the capsule is sectioned the tumor overflows. Because of the large ducts, if one spreads any part of the tumor it splits. It is a lesion so completely characteristic that there hardly is the need for microscopic confirmation in making the diagnosis.

We, then, can tell our patient from our knowledge of this lesion, its gross characteristics, and its microscopic appearance that she does not have a cancer. Our next question relates to what happens to these lesions if they are treated. We recently had an opportunity to study such a lesion in a woman of 79 years. She stated that the tumor had been present for 55 years. It was encapsulated and freely movable, although unusually hard. The duct system was atrophic, being similar to the normal breast tissue in the remainder of her breast. The fibrous stroma contained a collagen much denser than the normal breast, and there was no fat. Atrophy of the epithelium following menopause is the usual finding. Occasionally something else happens. During pregnancy a fibroadenoma may grow considerably in size, because it seems to be much more sensitive to the hormonal stimulation than the rest of the breast. Similarly, following lactation involution is much slower. Rarely there is epithelial stimulation. I think I have seen on at least one occasion a cancer arising from such a situation. I do not think that it is a very common outcome, however. Most of the cancers which one sees and which look as though they came from a pre-existing fibroadenoma are cancers which arose in the breast in which there is a diffuse fibroadenomatosis. It must be remembered that usually in the fourth decade or later fibroblastic proliferation is much more diffuse along the ducts and does not form the isolated nodule quite as frequently as it does in the younger person.

More common than carcinomatous change in the epithelium is sarcomatous change of the stroma. One often will see such a sarcoma developing around fairly normal looking fibroadenomatous ducts. As

such, it is called adenosarcoma. While it gives a better prognosis than fibrosarcoma in general, it should be considered a definitely malignant tumor. At one time I felt that a simple excision of the lesion in the breast was adequate treatment; but more recently I have encountered three patients with axillary node metastasis. I now feel that in the so-called adenosarcoma, or cystosarcoma phyllodes, it must be treated with radical excision. The diagnosis never is very difficult. These lesions sometimes are as large as an orange. They never are small. As a rule, there is a history of a long-standing fibroadenoma which has suddenly increased in size.

It is safe to say that the fibroadenoma should be removed because it is potentially dangerous and is simple to remove.

Often during the latter part of the third decade and early part of the fourth, many women begin to show an eccentric reaction in several areas of the breast. Ducts dilate and on cut section they resemble small cysts. At times the epithelium of this duct or cyst resembles that of a sudoriferous sweat gland. This seems to be a lesion typical of the human, although it has been produced experimentally by long-continued estrogenic stimulation in monkeys. No other animals seem to give that type of metaplasia. Along with the minute cyst formation, there occurs periductal fibrosis.

With the progression of time, the ducts become larger with much more periductal fibrosis and lobule formation disappears. All evidence of progesterone action leaves. With each menstrual cycle, these findings become exaggerated. With the periductal fibrosis, there often is tension with the attempted enlargement of the ducts and the patient often complains of pain and tenderness. This is exaggerated particularly shortly before the menstrual period. Obviously, the only way to prevent the pain is to prevent the increase in the size of the ducts, although great help often is afforded by support of the breasts with the proper type of brassiere. Methyltestosterone again sometimes is of great help in the treatment of that symptom. Examination of the patient's breast at such a period demonstrates what appears to be a fine nodular extension along the major ducts, often in a single small area but at times throughout both breasts. These nodules are not large, at times being only one millimeter or so across. However, at times three or four of them will coalesce and give the impression of a small hard irregular tumor. Often these areas must be excised in order to exclude cancer.

In the latter part of the fourth decade and the early part of the fifth, ovulation often ceases completely or else is extremely rare. Thus, there appears a marked preponderance of estrogen secretion. It is at this period that we encounter the so-called blue dome cysts. These may become very large. The cyst generally contains clear fluid and, microscopically, the epithelium, as a rule, is flattened. Many of them may be lined by epithelium of the sweat-gland type; and throughout the area of breast tissue adjacent the cyst, one encounters ducts of varying sizes. Rarely does one see evidence of lobule formation. Where involution has been rapid, areas of lymphocytic infiltration may be encountered.

Up to this point in our consideration we have paid relatively little attention to the numerous diagnostic terms used in the description of this disease. Such terms may be confusing. It is the understanding of the process that is important. So far, also, we have dealt with no evidence of epithelial overgrowth of any considerable extent. We have been concerned chiefly with abnormal duct formation and abnormal fibrous tissue reaction. What chance does a patient with such a disturbance have to develop a cancer when such lesions are present? Statistically, we perhaps would not be too far off if we said that ordinarily one woman out of every 200 will develop cancer of the breast. In the lesions which have been considered above, it is probable that about one woman out of 100 will develop cancer of the breast. Her chances of getting a cancer, regardless of whether or not the lesion is removed, therefore, are doubled. Yet, at the same time a one per cent chance of developing cancer in a particular viscus is a fairly slight chance and hardly warrants one being very radical in the treatment of such a lesion. If, therefore, we can exclude cancer, it seems rational to let these lesions alone because to treat them at all, in such a way as to prevent cancer, would require bilateral mastectomy. This does not to me appear to be justifiable.

Sometimes during the latter part of the fourth decade and the early part of the fifth, we encounter a complicated situation in the microscopic study of our benign lesions. This is one of epithelial overgrowth. This may present itself as a simple hyperplasia of the lining of the ducts, or the cells may grow in papillary form or even completely occlude the ducts. Such a lesion has been called carcinoma in situ. Again, it has been spoken of as a premalignant lesion. It, however, must be remembered that such a term does not necessarily mean that the lesion is destined to become malignant as is so often the case in similar hyperplasias of the epithelium of the stomach or of the rectum. Such hyperplasia may exist for many years with no evidence of invasion. If that epithelial overgrowth were to occur in a large duct just beneath the nipple, it would be considered as an intraductal papilloma. Where such overgrowth occurs in a large cyst, it is called an intracystic

papilloma. Where it occurs in the small or terminal ducts, it has been given the name adenosis, or Schimmelbusch's disease. All of these represent the same underlying lesion; namely, one of epithelial hyperplasia. As long as the growth does not invade into the breast stroma, it is considered benign. The moment that invasion occurs, it is considered malignant.

Let us now consider the probability of this group of lesions in which there is epithelial overgrowth of becoming malignant. This is a question which is hard to answer because many of the lesions are removed in their entirety for microscopic examination. Often enough, however, the lesions are multiple and many are left behind. I do not think one is too inaccurate to say that somewhere between five and 10 per cent of these patients from whom we have removed a lesion and studied it microscopically subsequently will develop cancer of the breast. This gives us a situation in which one person out of 10, or one person out of 20, definitely will develop a cancer. Therefore, here I think one must be more aggressive in his therapy. For this reason I feel that in this situation because we can never be sure that all of the hyperplasia is removed by the simple biopsy, the entire offending breast must be removed. In this judgment, many people would disagree.

The diagnosis of such epithelial proliferation before biopsy is not difficult to make if there is a discharge from the nipple. Where such a discharge from the nipple is bloody, one can rest assured that he is dealing either with epithelial overgrowth of the sort which we have described or else frank cancer. In a recent analysis of the patients seen at University Hospitals at the state University of Iowa, Donnelly noted that seven per cent of such patients with a bloody discharge had small duct proliferation, 31 per cent had duct papillomas, and 32 per cent had ductal carcinoma. Considered in another way, in those patients presenting themselves with bleeding from the nipple, half of them already had developed carcinoma and the other half presented a type of epithelial hyperplasia that often results in carcinoma.

Almost the same association was noted where a serous discharge was encountered. By serous discharge it must be understood that I am considering that type of fluid that is albuminous, clear, and resembles very much blister fluid. Where such a clear discharge or a bloody discharge exists in a patient beyond the fifth decade, it would seem to me that the burden of responsibility rests upon the physician who can exclude malignant or premalignant disease. I shall illustrate this with a particular example. Recently I was consulted by a patient 61 years old because of a serous discharge from her right nipple. She did not have a palpable mass that I could elicit. Because a woman at the age of 60 should not begin a serous discharge from her nipple without serious underlying difficulties, I elected to do a radical excision of her breast. When the entire breast was removed and sectioned, a small cancer approximately four millimeters in diameter was found invading the fascia of the pectoralis major muscle. It was so deep in the breast tissue that it could not be palpated externally. There also were several small metastases in the regional lymph nodes of the axilla. The entire duct system was involved in a diffuse hyperplasia. Here, then, was an instance in which the only revealing clue to the presence of a cancer was a clear, blister-like fluid coming from the nipple of a patient well beyond menopause.

I feel that our experience in a large series of patients who have had a clear serous discharge or sanguineous discharge from the nipple is enough to justify the radical approach in the handling of this kind of benign lesion.

If the nipple discharge is a lipid yellow or if it is green, milky, or brown, we as a rule are dealing with an entirely different lesion. Here we are not confronted with epithelial proliferation as much as we are dealing with a stagnation of duct secretions. As a rule, this is associated with cystic lesions discussed in the early portion of this paper. Here, then, the radical approach of excision of the breast is not justifiable.

In conclusion, may I say that it seems to me an impossibility for the surgeon to approach the problem of lesions of the breast adequately if he does not have a clear understanding of the underlying pathologic lesion. To remove the breast lesion, to send it to a pathologist, and to rely entirely upon a simple diagnostic term is inadequate. The surgeon also must look at his lesion grossly and microscopically. It is only in the understanding of the basic situation extant that the surgeon can give the proper care and the proper advice to the patient with a lesion in the breast. This makes it possible for him to individualize each situation. It makes it possible for him to be conservative when conservative measures are justified and radical when radical measures are indicated.

Current Progress In Clinical Cancer Chemotherapy

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There is at the present time not only theoretical interest in the possibility of developing chemical agents which might be effective in treating human cancer, but also considerable activity in a number of clinics throughout the country where such agents are being tested and their value estimated against a variety of neoplasms. There is a different attitude held now concerning chemotherapy than was the case even a few years ago.

In medicine, as in many other things, we have inherited much of the tradition and learning of the European schools. One of these concepts was that of "therapeutic nihilism," largely due, I believe, to Skoda of Vienna at the turn of this century. Many of you may have heard the saying which I am told was expressed in those days, i.e., "that if Rokitansky's autopsy findings confirmed Skoda's diagnosis, the patient had no right to complain." Today, however, *therapy* has taken its rightful place in importance alongside diagnosis, and the interest and effort expended in *cancer chemotherapy* is ever on the increase.

Since there are a number of substances which in recent years have been given clinical trial, at least to some extent, I have selected for brief presentation those which have been studied most thoroughly to date; but I will also mention some about which there is professional and public interest, although their standing as chemotherapeutic agents is at present still undecided or about which available evidence is at present not encouraging.

Hormones

(a) *Estrogens*

In 1943, Huggins,[1] shortly followed by Herbst,[2] reported that estrogens could be successfully employed in controlling a certain proportion of cases of prostatic carcinoma. The administration of diethylstilbestrol or ethinyl estradiol is followed in responsive cases by (1) decrease of metastases, (2) reduction in size of the prostate, (3) a fall in the serum acid phosphatase level, (4) relief of pain, urinary obstruction, and increase in the sense of well-being.[3]

It has been shown by Kahle[4] and his collaborators that the prostatic cancer cell undergoes definite degenerative changes following estrogen therapy, i.e., nuclear pyknosis, cytoplasmic vacuolization with subsequent fragmentation and disappearance of nuclear material, and finally, replacement by fibrous stroma, smooth muscle and round cells. A complete absence of cancer cells in the prostate after two years of massive doses of estrogen has been reported.

Bilateral castration produces about the same effects as estrogen therapy and appears to act more quickly than hormone therapy, when pain is used as a criterion. The comparative advantages of the two are still a matter of some debate, although there is a growing conviction that estrogen therapy in most cases accomplishes all that castration does, and in addition spares the patient the physical and psychic trauma of orchiectomy.

It has also been recommended that the doses of estrogen should be generous and continued throughout the life of the patient.

Estrogen therapy has also been tried for treatment of carcinoma of the breast in females. The best evidence to date for the results of such treatment is as yet inconclusive.[5] Definite regressions in the primary tumor, and lymph node and pulmonary metastases have been obtained; but these results are transient with considerable variation among patients. The most suitable cases are those 60 years of age or over, with contraindication in any patient who still menstruates or who has done so within a five-year period; in such cases acceleration of the rate of growth of the carcinoma frequently results. (Dose 5-20 mg./day of stilbestrol orally.)

(b) *Androgens*

Testosterone propionate, in cases of breast cancer with osseous metastases, has shown some promise particularly in pre-menopausal patients. (100 mg. parenterally, three times a week for ten weeks, then 60 mg./day for 10 weeks.) Symptomatic response comes in two to three weeks (relief from pain, increase in appetite, gain in weight).[5]

However, androgen or estrogen therapy cannot yet take the place of surgery in cases of mammary carcinoma which are still operable.

Nitrogen Mustard

During the late war it was found that a class of chemical agents known as nitrogen mustards had a pronounced damaging action on cells,[6] especially of lymphoid tissue. These compounds are closely related to mustard gas, differing in that nitrogen replaces sulfur. They exert a marked toxic action on the nucleus of the cell, with inhibition of mitosis and production of chromosomal abnormalities. The susceptibility of cells to these compounds appears to be related to their proliferative activity, and the effects are similar to those of radiation.

These nitrogen mustards are extremely toxic! Intravenous administration of these compounds in high enough dose can produce almost complete dissolution of lymphoid tissue in 24 hours. The bone marrow is also affected (especially the granulocytes) and with high enough dose complete aplasia can be produced. With large doses, degenerative changes in the epithelial tissues of the gastrointestinal tract occur and may result in a hemorrhagic enteritis.

It is possible to synthesize large numbers of "nitrogen mustards" but so far only two chemical congeners have been used clinically, bis (beta-chlorethyl) amine hydrochloride and tris (beta-chorlethyl) amine hydrochloride. Of these two the bis compound has been more extensively used since it appears to be less toxic and equally effective.

These drugs are readily soluble in saline and must be given intravenously and quickly (within five minutes), inasmuch as these compounds deteriorate rapidly. Because of intense irritation to the tissues, producing necrosis and sloughing if leakage takes place, and to lessen the possibility of thrombosis, the mustards are given by injecting the compound through the rubber tubing during an intravenous infusion of saline or glucose. The usual single dose 0.1 mg./kg. (with a maximum single dose of eight mg.) is ordinarily given on four consecutive days. There is some variation, but the limiting factor in determining dosage is the appearance of damage to the hematopoietic tissues.

The most satisfactory clinical results have been obtained in Hodgkin's disease.[7] In most cases there is significant temporary improvement; in some the improvement borders on the dramatic. Improvement is subjective (appetite and well-being) as well as objective, viz., rapid diminution of tumor masses, and reduction in size of the liver and spleen.

Such remissions, however, are usually brief, averaging two to three months, occasionally up to seven to eight months. Relapses generally respond to a second course of treatment, and several patients have been maintained in good health for two to three years by repeated courses at intervals of two months or more, as indicated. In a few cases, sensitivity to irradiation was thought to have been restored.

In lymphosarcoma[8] the results reported have been similar to those of Hodgkin's, but they are less regularly obtained and not so well maintained. Some improvement was observed in most patients and good effects in others, even after they had become resistant to radiation.

Cases of chronic leukemia have not responded so well as the diseases just mentioned, although in some instances results were obtained comparable to those following radiation.

I might also state that in polycythemia the effects with nitrogen mustard appear to be as good as those following radio-active phosphorus.

It appears from the clinical data obtained thus far, that the nitrogen mustards deserve a place in the treatment of Hodgkin's, to some extent in lymphosarcoma, and perhaps in some cases of chronic leukemia.

They possess these advantages over radiation:

1. Results are obtained more quickly.
2. They are effective in some cases that are radio-resistant.
3. G.I. disturbances are usually not so severe.

Urethane

About the time the nitrogen mustards were discovered to have their cytotoxic action, the English investigators were focusing their attention on a compound, urethane. Urethane had been synthesized and used a long time ago (1834) as a hypnotic, but later was supplanted by the barbiturates and other drugs.

The work by Templeton and Sexton on plants, and later by Haddow and Sexton on animal tumors led to the clinical trial of this drug by Paterson and her co-workers,[9] which was soon followed by its use in this country. The results of the last three years or so have established urethane as having a place in the treatment of proliferative disorders of white blood cells, particularly in chronic myelogenous leukemia.[10] In relatively early cases a remission may be obtained and maintained for at least a few months; but there is quick relapse when the drug is discontinued. The effect of urethane is much like that of radiation; and in advanced cases roentgen therapy is superior to urethane.

Stilbamidine and Pentamidine

Chemotherapy has also been tried in the case of another type of malignancy, i.e., multiple myeloma. The compounds stilbamidine and pentamidine have been used for this purpose by Snapper[11] and others.[12] These compounds had been used in kala-azar, and Snapper tested their effectiveness in myeloma on the association of the increase in the serum globulin which frequently happens in the two types of disease. In conjunction with a low protein diet, found essential for maximum effect, these compounds produced improvement, notably relief of pain. Treatment merely checked the disease, and relapses occurred. An interesting cytologic finding was the presence in the cytoplasm of myeloma cells of precipitates of ribosenucleic acid. The significance of this phenomenon is still to be determined.[13]

Folic Acid Antagonists

Some years ago Lewisohn and his collaborators

reported that the injection of various extracts (spleen, barley, yeast) resulted in the disappearance of a certain proportion of spontaneous mammary carcinomas in mice. Later it was shown that similar results could be obtained by administration of *Lactobacillus casei* factor derived from liver.[14] Due to the work of Subbarow and his associates a form of folic acid, the "fermentation folic" was later isolated and then chemically synthesized.

Farber and his collaborators[15] at the Children's Hospital in Boston, following the work of Lewisohn, obtained partial remissions in a small percentage of cases in various types of malignancy following the use of folic acid conjugates notably diopterin and teropterin. The results, however, were variable and not satisfactory. The same experience with these substances was encountered by other workers, i.e., slight and temporary remissions or none at all.

However, Farber noticed that at times in children with acute leukemia there was an exacerbation of the disease following treatment with folic acid. It was therefore decided that it might be worth while to test folic acid antagonists for possible effect. A number of such compounds with antifolic properties have been given clinical trial, i.e., aminopterin, a-methopterin, amino-an-fol.

In the hands of Farber and his associates,[16] and in the hands of others in different clinics throughout the country, definite, although temporary remissions have been obtained in acute leukemia in children by the use of these compounds. They are, however, toxic—and not recommended as yet for general use by the practitioner. Deaths have been recorded in a number of cities, following the injection of these compounds. Moreover, it is now known that patients who have received testosterone cannot tolerate the usual amount of aminopterin; and deaths have occurred in patients, previously treated with this androgen, following doses of aminopterin they otherwise could have tolerated.

Remissions obtained may last from a few to many months, and the percentage of patients who respond varies from zero to 50 per cent.

It is being appreciated that the action of this folic acid antagonist is not a simple anti-folic action, since large doses of folic acid fail to counteract toxic symptoms following administration of the antagonist.

Bacterial Polysaccharide

The use of bacterial metabolites in treating malignancy goes back about 100 years. In this country Coley introduced the use of his "toxin" in 1891, and although he himself persevered in his belief in, and use of, this preparation as capable of exerting an ameliorating action in the course of the disease, the profession abandoned it after a trial by some, and practically nothing was done with this type of substance for a long time.

About 15 years ago, attention was once again directed to this type of research, and since then, largely through the effort of Shear and his collaborators, a polysaccharide has been isolated from *E. coli* and from *Serratia marcesens* which is effective in damaging animal tumors in relatively small dose.[17,18]

This polysaccharide has been given some clinical study and, as shown by biopsy before and after administration, has been found to induce necrosis in some types of human tumors, such as fibrosarcoma, chondrosarcoma and lymphomas.

Although it affords us a promising lead, its clinical use is not recommended because of its toxicity. Gastro-intestinal disturbances, onset of fever and production of marked fall in blood pressure necessitate the most careful clinical management of the patient,[17,18] even in clinical researches with these materials.

I should like now to mention a few substances which have aroused considerable professional and public interest from the standpoint of treating cancer, but about which there is no justifiable evidence concerning their value in this respect. Possibly some of you have been consulted by your patients concerning them and their use in treating malignancy.

1. AF-2

Information about this substance came from Italy through an American-Italian newspaper. From the meager information available, it is a "serum," devised by a Prof. Francisco Guarnieri, prepared from the livers of "cancer-resisting" animals i.e., goats, pigs, sheep. No data have been available, from either tumor-bearing animals or patients, in support of the claims advanced.

2. H.11

In 1930,[19] Thompson (from England) reported that an acid-alcoholic extract of parathyroid glands retarded the growth of transplated Twort carcinoma in mice. Later it was stated that a substance possessing similar ability could be extracted from normal male urine. It is this substance, derived from this source, which was designated as H.11.

Recently Williams[20] presented the results of over 1300 cases of human malignancy treated with H.11 and claimed that in 63 per cent of this number there was clinical evidence of regression or arrested growth of the tumor.

In 1944, the British Medical Research Council appointed a committee[21] to assess the evidence on which claims for H.11 were based. The committee conducted its inquiry by (1) an examination of case histories supplied by the Hosa Laboratories (which produce H.11) and (2) an experimental

investigation on the effect of H.11 on various tumors in mice, including those used by the originators of H.11.

The committee's conclusions were (1) that it was not possible to deduce from an analysis of the clinical records that H.11 had any effect either on the rate of growth of cancer in man or on the clinical course of the disease and (2) experiments on tumors in mice carried out under direction of Hosa Laboratories could not demonstrate any tumor inhibiting action by H.11.

3. KR

Fo the past several years Roskin and his associates (Russia) have been publishing positive findings with regard to the therapeutic use of an endotoxin prepared by lysing *Trypanosoma cruzi* (Chagas' disease). Successful results have been claimed for several types of human malignancy as well as in experimental tumors of various kinds.

A number of attempts at experimental confirmation of this investigation have been made. Perhaps the most extensive have been those of Hauschka and his collaborators.[22] These investigators have used endotoxin as well as infecting tumor bearing animals with living organisms.

No effect was obtained following the use of endotoxin. Some retardation was obtained in tumor bearing mice following infection with the living organism; but this appeared to be non-specific as it was accompanied by loss in body weight and parasitemia of vital organs. When the disease was brought under control by drug treatment, the tumor resumed growth. Cancer cells were rarely parasitized.

At the National Institutes of Health a survey was recently completed in which KR prepared from eight different strains of T. cruzi (including the Wellcome strain used by Roskin) were tested against a transplanted mouse sarcoma (S.37). No tumor retarding effect was found.[23]

At the present time, about a half dozen investigators throughout the world have reported negative results in attempts to confirm Roskin's findings. The single exception, a paper by Malisoff, cannot be considered as tenable for several reasons, as has been stated by Hauschka.[24]

For the interested person, attention may be drawn to an informative editorial in the Journal of the American Medical Association in which the alleged value of several so-called cancer cures is discussed.[25]

It has been evident, in this brief review of chemical agents which have been given some clinical study, that there has been no mention of a "cure." To date there have been no "cures." At best there is palliation, remission for a few weeks, or in most favorable cases perhaps for several months.

Nevertheless, the question today is no longer "is cancer chemotherapy possible?" The encouraging fact is that it *has been done*—but within limits. So far the limits are disappointingly restricted, compared with our objective. Our aim now is to extend those limits to an ever wider degree until chemical substances which can produce increasingly beneficial and more lasting results to the patient become available.

I don't know when such a realization of our aim will be achieved. My feeling is that it will be a long and thorny road, but I am optimistic enough to believe that with laboratory and clinic collaborating in the long hard drive, that day will come.

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The Treatment of the Leukemias and the Malignant Lymphomas

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While, practically speaking, leukemia and malignant lymphoma remain incurable diseases, we have reason to hope that the continued combination of efforts of men working in the clinical and experimental fields may yet provide us with more useful answers to the questions that puzzle us.

In the clinical field, therapeutic efforts at the present time consist essentially in the administration of various cytotoxic or clearly destructive agents in the rather forlorn hope that these substances will do more damage to the neoplastic cell than to the normal cell. As yet the differential in degree of vulnerability has been too fine to permit more than some deceleration of the neoplastic process.

In considering the value of so-called therapeutic agents in cases of leukemia and malignant lymphoma one must remember the decided variability of the clinical course pursued by each individual case before attributing changes to specific efforts on the part of the physician. To my knowledge there is on record no "control" series of untreated patients having either type of disease. However, all of us have from time to time observed occasional patients who somehow escaped specific therapy but nonetheless prospered, in a relative sense.

With the exception of certain well-localized forms of malignant lymphoma there is no incontestable evidence that the therapeutic measures to be discussed result in prolongation of life, although there can be no doubt that palliative relief of considerable, if temporary, degree fairly consistently follows their application.

Surgery

While the established case of malignant lymphoma usually presents the characteristics of a widespread disease, there is considerable evidence to indicate that early lymphosarcoma or Hodgkin's disease, particularly the paragranulomatous variety, may be a localized process. Surgical extirpation of such lesions has resulted in apparent "cure" in an encouraging number of instances. This has been particularly true in cases of lymphosarcoma of the head and neck.

This experience, (as reported by Hellwig[1], Gall[2], Rhodes[3] and others) emphasizes the urgency of early diagnosis in such cases if anything more than palliation of symptoms is to be offered, since extension of the process may occur rapidly. In substance this means that one must expedite the biopsy study of any unexplained enlargement of lymph nodes. It may be reasonably suggested that tonsillectomy in adults be followed routinely by microscopic examination of the tissue, since lymphosarcoma not uncommonly arises in the upper part of the respiratory passages.

While one should be on watch for patients possibly amenable to surgical therapy it is unfortunately true that the great majority of patients will not qualify for this type of management.

Irradiation

A. *Roentgen Irradiation.*—After 45 years roentgen irradiation remains the most widely employed and most consistently satisfactory means of producing clinical remissions in this group of diseases.

(1) Chronic Leukemia.—Pressure symptoms, anemia and general systemic manifestations constitute the common indications for treatment. There is no reason to feel that "prophylactic" administration of roentgen rays or other agents significantly slows the progress of leukemia. Treatment may be wisely withheld in asymptomatic cases. This is particularly true in chronic lymphatic leukemia in the older age groups, wherein the disease is often relatively benign and patients die as often "with" the disease as "of" it.

The response in patients with symptoms is generally best in the myelogenous type. Symptomatic lymphatic leukemia is less dramatically influenced and monocytic types of the disease obtain a satisfactory remission less often than either. In general, the morphologic types respond in similar degree to the other therapeutic agents employed.

Variations in technic of administration seem relatively unimportant—good results having been obtained by experienced therapists with various methods—and should be tailored to fit the individual case.

The duration and amount of treatment in a single course are determined by the clinical and hematologic response as estimated by daily examinations and leukocyte counts.

Remissions last for variable periods, usually three to six months. Treatment is repeated on development of signs of imminent relapse.

Refractoriness eventually becomes apparent in all cases. Other agents than roentgen rays may be temporarily effective thereafter but none are consistently so.

Despite the low leukocyte count in cases of leukopenic leukemia a fairly wide margin of safety ap-

pears to exist and roentgen radiation can be safely and beneficially administered if the results are carefully observed.

Irradiation sickness is unfortunately a common accompaniment of this form of treatment, being particularly severe with irradiation over the upper part of the abdomen.

(2) Acute Leukemia.—Cautious therapy may be administered locally in the occasional case with distressing pressure symptoms but roentgen radiation is ordinarily useless and possibly harmful.

(3) Malignant Lymphoma.—Roentgen therapy may result in a dramatic temporary remission of symptoms within a period of very few days.

Again the technic employed should be fitted to the needs of the individual case. Systematic, segmental exposure of all possibly involved areas is carried out and definite sites of disease are more aggressively attacked.

The amount and duration of therapy depends on the response and tolerance of the individual patient. Relatively acute forms must be treated with caution.

Refractoriness eventually develops in all cases, earlier in the more malignant varieties, although these may respond encouragingly in the beginning. When the process has been well localized and treatment has been aggressively administered, occasional "cures" may follow.

B. *Radium Irradiation.*—This has been employed but it offers no advantages of consequence, is available in too few localities and is a relatively expensive form of treatment.

C. *Radioactive Isotopes.*—During the past ten years radioactive isotopes have been employed in the treatment of neoplastic diseases. Radioactive phosphorus, P^{32}, has been used most extensively in treatment of disorders of the hemopoietic system.

In leukemic mice the greatest concentration of P^{32} was found in the infiltrated bone marrow and tissues such as the lymph nodes, liver and spleen. However, the leukemic cells were found to contain only two to three times as much of the isotope as the normal cells[4]. Studies on thyroid carcinoma indicate that preferential absorption by neoplastic tissue may have to reach a level of 50:1 as compared with normal cells if control of the growth is to be effected[3].

P^{23} may be administered orally or intravenously. It has not provoked irradiation sickness. Theoretically, it provides a means of exposing neoplastic tissue to beta radiation for extended periods and it should reach all foci of disease.

(1) Chronic Leukemia.—In chronic myelogenous leukemia the therapeutic results of P^{32} in general have been similar to those obtained with roentgen radiation[5]. As with roentgen therapy, results have been more remarkable in cases of myelogenous leukemia than in lymphatic or monocytic leukemia. Enthusiasm has been dampened at the Mayo Clinic by the occurrence of acute leukemia as the terminal event in 79 per cent of the cases of chronic leukemia in which P^{32} was used. Such a development may be anticipated in approximately 30 per cent of cases in which roentgen therapy is used. One cannot comfortably expose patients who have chronic leukemia to treatment that appears to promote acute regression of the process.

(2) Acute Leukemia.—P^{32} has not been shown to alter the clinical course of such cases beneficially.

(3) Malignant Lymphoma.—Encouraging results have been occasionally reported but the great majority of patients have responded poorly.

Chemical Agents

A. *Nitrogen Mustards.*—As a result of extensive studies during World War II knowledge of the effect of these substances on various tissues was extended. When administered in sublethal dosage the action of the mustards was most pronounced on those tissues which normally are actively proliferative, particularly the mucosa of the gastro-intestinal tract and the hemopoietic organs.

The over-all effects are quite similar to those of roentgen radiation. In solution these substances form a cyclic cation with liberation of chloride ions. Apparently, this cation interferes with the operation of certain cellular enzyme systems, inhibits mitosis and may produce chromosomal abnormalities. The action is short-lived and a region is completely protected if its blood supply is interrupted for five minutes after the injection of nitrogen mustard[6].

The relatively selective action of these substances on hemopoietic tissue led to preliminary trial in leukemic and sarcoma-bearing mice and finally to use in the clinical field.

An intravenous injection of 0.1 mg. per kilogram of body weight (methyl-bis-(beta-chloroethyl)-amine hydrochloride is commonly used) daily for four consecutive days constitutes the customary course[7]. Toxic effects in the form of nausea, vomiting and occasionally diarrhea consistently follow within two to four hours of the injection but rarely cause serious difficulty. More important is the common depressant effect on bone marrow activity, the degree depending on its pretreatment status and the size of the dose. Marked leukopenia and thrombocytopenia may follow. However, recovery in most cases is rapid and apparently complete, usually permitting another course of treatment within five to six weeks.

(1) Chronic Leukemia.—Remissions, clinically and hematologically similar to those produced by roentgen radiation, have been produced in early cases. Treatment in advanced cases has been uni-

formly fruitless and, in view of the possibility of grave damage to remaining normal marrow elements, it may be harmful.

(2) Acute Leukemia.—The nitrogen mustards have no demonstrable value in treatment of these problems.

(3) Malignant Lymphoma.—Hodgkin's disease, including some advanced and roentgen-ray resistant forms of the disease, has been most benefited by treatment with the nitrogen mustards. The results have sometimes been spectacular and remissions lasting a few weeks to several months have been consistently produced. Systemic manifestations rapidly subside, followed by shrinkage of lesions in hemopoietic and other organs. The average remission has, however, been shorter than that produced by roentgen radiation and certain local lesions respond less favorably. Repeated remissions may be produced and sensitivity to roentgen radiation has been restored in some instances[6, 7]. Nitrogen mustard has been found useful when employed as an adjunct to roentgen radiation in cases with systemic and localized manifestations of the disease.

In lymphosarcoma results have been similarly beneficial in about 30 per cent of cases[6]. In the highly malignant forms of the disease treatment with nitrogen mustard has been relatively ineffective.

Other more effective and less toxic substances of this type may be introduced in the future, but it seems overoptimistic to hope that they might possess the degree of selective activity demanded of a curative agent.

B. *The Urethanes.*—Leukopenia was observed as a side effect in patients and experimental animals under treatment with the urethanes for various neoplastic diseases[8]. As a result, these substances were given a therapeutic trial in leukemia and were found to have some palliative effect[9].

Studies in mouse and human leukemia indicate that urethane (ethyl carbamate has been most widely used) acts as a mitosis arrester. Its greatest effect is exerted on cells at an immature stage of development[10]. Megakaryocytes are more resistant than other bone marrow elements. Leukemic foci in various organs may be reduced in extent. These changes are, however, inconstant and may not occur despite marked changes in the peripheral blood picture. The changes noted are roughly similar to those provoked by roentgen radiation or nitrogen mustard.

Urethane may be given orally in a dosage of two to three gm. daily until a reduction in the total leukocyte count occurs. This usually requires a period of 10 to 30 days of treatment. Thereafter the dosage is adjusted in an effort to maintain the total leukocyte count at near normal levels[11]. Hematologic relapses often occur within 10 to 20 days if treatment is discontinued and efforts to reinstitute control may be thwarted by the appearance of a refractory state.

Anorexia, nausea and vomiting (from gastric irritation) are the difficulties most commonly encountered in the course of treatment. These symptoms may be controlled by a reduction in dosage and it is not often necessary to discontinue treatment entirely on this account. Severe bone marrow depression has been reported as a result of therapy with this substance[12]. However, such a misfortune is apparently a rare complication if the dosage is properly controlled by periodic studies of the blood. Urethane seems to be a less toxic agent than other agents used in the chemotherapy of leukemia and malignant lymphoma.

(1) Chronic Leukemia.—In chronic leukemia, particularly of the myelogenous variety, urethane may effect a remission clinically and hematologically similar to that resulting from roentgen therapy. The results, are, however, less consistently produced and have been well sustained in only a third of the patients treated (Table 1). As is the rule with all palliative agents, best results are obtained in early phases of the disease. Relapse under treatment may occur and in some instances hematologic changes of an encouraging character were accompanied by all evidences of clinical failure. At present observations are in progress to determine if remissions induced by roentgen radiation can be prolonged by interim therapy with small doses of urethane.

Table 1

Urethane (Ethyl Carbamate) In Treatment of Chronic Myelogenous Leukemia

Result	*Cases*
Satisfactory response	11
Early improvement followed by refractory state	11
No significant change	5
Worse under treatment	6
Total	33
Deaths	9

(2) Acute Leukemia.—The course of acute leukemia is not appreciably influenced by treatment with urethane.

(3) Malignant Lymphoma.—Urethane has no demonstrably consistent effect on the clinical course of Hodgkin's disease or lymphosarcoma, although enlarged lymphoid structures may be reduced in size.

C. *Arsenic.*—Therapy of chronic leukemia with arsenic in the form of Fowler's solution (potassium

arsenite) should be briefly mentioned since there has been some recent revival of interest in its use. It has been most effective in treatment of chronic myelogenous leukemia and produces remissions fairly consistently. Occasionally it has some effect in roentgen-ray refractory cases. Relapses quickly follow when medication is discontinued.

The pruritus of Hodgkin's disease may sometimes be alleviated by treatment with Fowler's solution.

Arsenic has the advantage of ready availability and is less expensive than other forms of treatment. However, its toxic effects are often troublesome and sometimes serious.

Antivitaminic Agents (Folic Acid Antagonists)

Whereas the clinical effectiveness of the agents previously discussed was learned incidentally or as the result of trial of substances having relatively nonspecific cytotoxic properties, folic acid antagonists were devised as a therapeutic agent for acute leukemia on a somewhat more rational basis.

Farber and associates[13] reasoned that folic acid antagonists might be of value in the treatment of acute leukemia after observing postmortem evidences of an acceleration of the leukemic processes in patients who had been treated with folic acid or folic acid conjugates. SubbaRow and others[14-16] developed a series of folic acid antagonists with the assistance of cultures of Streptococcus faecalis, the normal growth of which is dependent on the presence of folic acid.

Aminopterin (4-aminopteroylglutamic acid) is the most potent substance available at present and has received the widest clinical trial.

Farber and his associates[13] observed clinical and hematologic remissions following administration of this substance in 10 of 16 cases of acute or subacute leukemia in children. At the Mayo Clinic five of 18 children but only one of 23 adults have been similarly benefited[17].

The results are sometimes spectacular, with striking clinical improvement accompanied by a restoration of a hematologic picture approaching normal. The improvement has been sustained for periods of months in some instances but relapse has eventually occurred after treatment has been discontinued.

Aminopterin exerts decided toxic side effects: ulcerative stomatitis, anorexia, crampy abdominal pain, bloody diarrhea and alopecia have developed when treatment is carried on long enough to influence the blood picture materially. In some instances extreme marrow pancytopenia has been induced[13, 17] and apparently sometimes has hastened the patient's death. However, development of marrow pancytopenia may be followed by recovery of the marrow and remission as described previously. An interesting side effect on the erythrocytic elements of the marrow has been the occasional conversion of normoblastic cells to a type resembling the megaloblasts of pernicious anemia[17].

While it may be reasonably hoped that continued investigations of this type will eventually lead to a better understanding of the leukemias, it should be emphasized that no cures have resulted from treatment with aminopterin and that in adults even temporary remissions have been rare.

Summary

Numerous agents are available which exert a measurable palliative effect on the course of chronic leukemia, but none demonstrably prolong life.

There is at present no satisfactory means of treating acute leukemia although our long-standing hopelessness in regard to such cases has been somewhat modified by the recent clinical introduction of the folic acid antagonists.

Early diagnosis, followed by surgical removal of diseased tissue or aggressive local roentgen radiation or both, offers the only hope of cure in cases of malignant lymphoma at the present time.

Some studies now in progress at the experimental level suggest that a widening variety of therapeutic agents may be introduced and perhaps the outlook for the unfortunate victims of these diseases may be considerably brightened.

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